

APPLICATIONS OF
COMPUTATIONAL CHEMISTRY AND
RELATED METHODS TO PROBLEMS IN
HETEROCYCLIC ORGANIC CHEMISTRY

BY

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1987

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THIS WORK IS DEDICATED TO

DR. J. COTTER HIRSCHBERG

AND

FATHER JOHN GILLESPIE

ACKNOWLEDGEMENTS

This work could not have been accomplished without the help of many people, only a few of whom, mentioned below, whose efforts can be acknowledged here.

This research could not have been initiated, nor sustained and brought to a successful conclusion, without the patience and wisdom of Professor Alan R. Katritzky, who served as my research director. Also very important in this regard is Professor Michael C. Zerner, who supplied computer time and advice on theoretical problems encountered.

Special thanks go to Professor Samuel B. Trickey, who took time from a horrendously busy schedule to give my (revised) dissertation a very close reading which was extremely helpful to me.

Comments made by Professors Yngve Ohrn, Bill Jones, and Merle Battiste, in the course of the research and during the actual writing-up, were much appreciated.

Professor Eric Enholm supplied a computer program which enabled me to make publication-quality illustrations for the entire dissertation in less than 10 hours.

Thanks also go to Drs. Steve Cato, Danuta Rasala, and Kathy Laurenzo for reading the manuscript and offering comments on it.

Ms. Mary Crume of the Editorial Office at the Graduate School has my thanks for compiling a list of the (numerous) errors committed by me in the first version of this dissertation, thus making it easier for me to get it right the second time.

It is impossible to endure the process of doing research and writing a dissertation without the constant aid of friends, only a few of whom are mentioned here: Dr. Erik Farley, Kris Tilford, Laura Carpenter, Chuck Wesolowski, Paul Staudhammer, Chris Westley, Jeanne Golay, David Low, Tate Clair, Rodney Mullen, Scott Mahaney, Michael Martin, Michael Murphy, Var Thelin, Michael Koretsky, Charles Wing, David Ciaffardini, Joe Reineke, Pete Sapia, Wade Hines, and Patrick Hughes. Many others have helped, but there is simply not enough room to list them all.

Finally, I thank my parents, Mrs. J. N. Polallis, and Mr. Hudson H. Luce, Sr., for their constant support and encouragement.

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Abstract of Dissertation Presented to the Graduate School
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December 1987

Chairman: Alan R. Katritzky
Major Department: Chemistry

A well-known and widely disseminated computer program package (AM1/MNDO), designed for laboratory use by chemists for semi-empirical molecular orbital calculations, is utilized in this study to help provide insights into problems in which conventional modes of reasoning, such as chemical intuition, electron pushing, and/or frontier orbital theory, give results not in accord with experiment.

Calculations made with this program are made assuming that the molecule does not significantly

interact with other molecules, but this assumption may not hold with the experimental conditions. Four problems are analyzed in detail. The first is the computational rationalization of anomalous orientation of nitration in a series of N-phenyl substituted heteroaromatic compounds using a variation of the Fukui frontier orbital method, the second is an analysis of possible reasons for formation of a non-benzenoid tautomeric product in a reaction where the benzenoid product is expected, the third is an attempt to explain the counterintuitive formation of an isomer of a tricyclic saturated heterocyclic compound which has two seven-membered rings fused onto a central six-membered ring, and the fourth problem is an analysis of the importance of dipole stabilization in describing and explaining the stabilization of certain carbanions.

In conclusion, the results obtained through the calculations help to rationalize the phenomena explored to various degrees, from a very limited amount in the case of the tricyclic systems, to a fair extent, in the case of the N-phenyl substituted heteroaromatic compounds.

CHAPTER I GENERAL INTRODUCTION

1.1 Introduction

Organic chemists, in their work of devising new syntheses and of understanding the mechanisms that underlie the reactions that comprise the synthetic routes used, utilize a combination of "chemical intuition" gained from experience and empirical knowledge of the chemistry of the compounds with which they work, and simple electronic theory. In some cases, these tools do not suffice to provide an explanation for what might have happened in a chemical reaction or synthesis, and other means, such as the calculation of molecular geometries, orbitals, and other related quantities, must be resorted to. Even when calculations are performed, their interpretation may not be straightforward, and so new ways of looking at the calculated results must be devised. This work concerns three problems in heterocyclic organic chemistry for which the usual methods of analysis break down and also contains a study of the relative contribution to overall stability, and the mechanism of that

stabilization, afforded by a certain functional group when adjacent to a carbanion. Calculations were performed, and some new ways of looking at the results in relation to the problem at hand were used.

In order to get a better look at how organic chemists usually reason about reactions and mechanisms, a short explanation of the intuitive method known as electron pushing is useful, along with examples of its use. An example of the simple electronic theory used by organic chemists is given next, and then a brief outline of the general concept of the work is presented. Finally, a brief introduction is provided for each of the problems studied.

1.2 Intuitive Tools: Electron Pushing

1.2.1 Introduction

The combination of intuition and elementary theory is applied by organic chemists to the problems at hand, by way of a very simple, yet extremely powerful intuitive tool called "electron pushing." Electron pushing is a book-keeping device for electron pairs, in which curved arrows symbolize the flow of

electron pairs during a reaction. A "reaction mechanism" is a sequence of these reactions, each of which involves a transformation in which bond formation or cleavage follow sound chemical principles. Some of the principles which will be used here are valency and the octet rule, balance of formal charge, electronegativity differences, resonance effects, steric crowding effects, acidity and basicity, and oxidation state.

1.2.2 Valency and the Octet Rule

The mental construct which forms the basis for the octet rule was first devised by G. N. Lewis in 1902 as a model for the inner structure of the atom, in which the electrons in the atom are arranged in concentric cubes about the nucleus, with the electrons located at the vertices of the cubes. In a further refinement of the rule [16JA762], the following postulates are given:

1. Each atom has a kernel or formal nucleus which contains an excess of positive charges corresponding to the ordinal number of the periodic group to which the element belongs.

2. The atom is composed of this formal nucleus and an outer [valence] shell which contains electrons equal in number to the excess of positive charges in the kernel. The number of electrons in this outer shell is allowed to vary between zero and eight during a chemical change such as an oxidation or reduction.

3. The atom tends to hold an integral number of electron pairs in the shell, and most of all, to hold eight electrons, which are normally in a symmetric arrangement.

4. Two concentric atomic shells are mutually interpenetrable.

5. Electrons are not held in distinguishable positions at the corners of the cube, but are held in position relative to the nucleus by forces which are determined by the nature of the atom and the other atoms around it.

6. Forces between particles at very close ranges do not obey the inverse square law.

The octet rule as it is known today was first stated by Lewis in 1923 [23MI79]. The tendency for every atom to form an arrangement with eight electrons in the outer shell is noted, then a rule is given by which two atoms, bonded to one another, may conform

with the octet rule: "Two atoms may conform to the...octet rule, not only by the transfer of electrons from one atom to the other, but also by sharing one or more pairs of electrons. These electrons which are held in common by two atoms may be considered to belong to the outer shells of both atoms."

The octet rule as used in electron pushing is that each atom in a Lewis structure (see Figure 1.1)

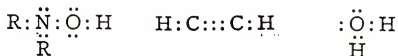


Figure 1.1: Lewis Structures

may be surrounded by at most eight electrons, whether they be in lone pairs or shared between atoms. This rule is most useful for compounds with constituent atoms from the first and second rows of the periodic table, since elements in succeeding rows have d-orbitals available for bonding. In electron pushing, the elements in succeeding rows are treated as their counterparts in the second row, so that Cl, Br, and I are treated in the same way as F, and S and P are treated in the same way as O and N, respectively. A

modification to the Lewis octet rule is used, in which there are four available orbitals, each of which can be filled by a pair of electrons, in the outer [valence] shell. Boron is trivalent with three valence electrons and C is tetravalent with four valence electrons. Since there are only four orbitals available, atoms with more than four valence electrons must have at least one orbital with electrons paired, so that N is trivalent with one lone pair, O is bivalent with two lone pairs, and F is univalent with three lone pairs (see Figure 1.2). Hydrogen, in the first row, has one valence electron and so can form only one shared electron-pair bond. A short-hand form for writing a shared electron-pair bond is to draw a line between the atoms bonded, in place of the two dots, as in Figure 1.1.

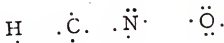


Figure 1.2: Elements for Lewis Structures

1.2.3 Formal Charge

The formal charge on an atom can be computed using the following formula:

$$\text{Charge} = N - (S/2 + 2*LP)$$

where N is the number of valence electrons of the atom, S is the number of shared electrons between that atom and any others, and LP is the number of lone pairs on the atom. The formal charge can also be calculated by drawing a Lewis structure, and dividing shared electrons equally amongst the bonded atoms. The electrons around each atom are counted and compared to the number of valence electrons for the free atom in its neutral un-ionized state. The formal charge for each atom is the number of the electrons of the free atom minus the number of electrons in the bonded, "disconnected" atom (see Figure 1.3). The first presentation of the idea of formal charge was made by Langmuir in 1921 [21S59]. For each electron pushing equation drawn, the formal charges on each side must

balance, in order to ensure the conservation of electrons.

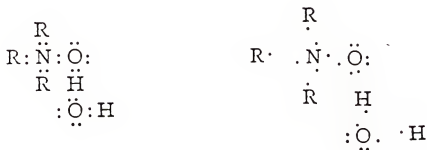


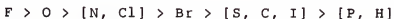
Figure 1.3: Formal Charge Calculation

1.2.4 Electronegativity

Electronegativity as used in this context is a qualitative measure of the ability of an atom to attract electron density. If the atom on one side of a shared electron-pair bond has more electron density near it than the atom on the other side, then the first atom is said to be more electronegative than the second. This concept was foreshadowed by Lewis in 1923, in his analysis of halogen-substituted carboxylic acids [23MI139], and more fully developed by Pauling in 1932 [32JA3570] from a study of the bond strengths of

various bonds using experimentally determined heats of formation.

The relative scale of electronegativities used here is:



For example, most of the electron density in the C-F bond would lie near the F atom, with F said to bear a partial negative charge, and C a partial positive charge. The dipole moment of a compound arises out of this bond polarization.

1.2.5 Resonance Effects

Resonance is a concept used in electron pushing to assess qualitatively the relative stability of a system with delocalized electrons. A discussion of the theoretical background of resonance effects was published by Pauling in The Nature of the Chemical Bond [60MI1]. The fundamental principle of quantum mechanics used is that the energy value W_0 calculated using quantum mechanical methods with the use of the exact wavefunction ψ_0 is less than that found with any other

wavefunction ψ that might be used, so that the actual geometric structure of the ground state of the system is that which gives the system its maximum stability. For example, two structures, I and II, are considered, which might both represent the ground state of some molecule. If the wavefunctions of states I and II are each multiplied by a suitable constant and summed to form a new wavefunction, the new wavefunction is also a valid wavefunction for the system:

$$\psi = a\psi_I + b\psi_{II}$$

The value of b/a that gives the energy its minimum value can be found by calculating the energy corresponding to ψ as a function of b/a , and by the fundamental principle of quantum mechanics given above, the corresponding wavefunction is the best approximation to the exact ground-state wavefunction which can be formed by this method. If the optimum value for b/a turns out to be either very small or very large, this denotes that the ground state of the molecule is best represented by structure I, or structure II, respectively. In cases where the value of b/a is close to unity, the best wavefunction is formed

in part from both ψ_I and ψ_{II} and so the ground state of the system is best described as involving both structures I and II, or as a resonance hybrid of I and II. In his discussion of the resonance energy, Pauling goes on to say that the structure of the system is not exactly intermediate between the resonance structures, which would result in the ratio b/a being exactly equal to unity, due to the energy of stabilization (resonance energy), which is the extra stability relative to the most stable resonance structure arising from the interaction of the two resonance structures and the energy difference between them.

The number of contributing resonance structures can be greater than two, as below. Their relative contribution is found by minimizing the energy with respect to the coefficients.

$$\psi = a\psi_I + b\psi_{II} + c\psi_{III}$$

In electron pushing no calculations are performed, and so resonance structures must be drawn using chemical intuition and experience of which structures are chemically reasonable, and which are not.

Idealized, non-existent structures, so-called resonance contributors, are drawn according to the rules given below. The species with the greatest number of reasonable resonance contributors is held to be the most stable. The rules are as follows:

1. Each resonance contributor has the same spatial arrangement of atoms. The only thing that changes is the electron density about those atoms (see Figure 1.4).



Figure 1.4: Spatial Arrangements for Contributors

2. The octet rule must be obeyed for the first- and second-row atoms, and to the extent possible for the elements in the succeeding rows.

3. The electronegativity scale of atoms given above must not be violated by the candidate contributor. For example, positively charged oxygen with six electrons surrounding it, and carbon atoms

bonded to each other, each in the same electronic environment, one bearing a negative charge, and one bearing a positive charge, are not features seen in good resonance contributors (see Figure 1.5).

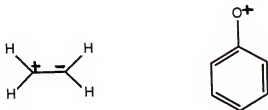


Figure 1.5: Violations of Electronegativity Scale

4. More resonance stabilization is attributed to structures which avoid artificial localization of charge, i.e. breaking of a bond into one negative and one positive charge, than those structures which depend on such localization (see Figure 1.6).

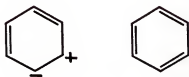


Figure 1.6: Artificial Localizations of Charge

5. Resonance stabilization is held to be greatest when there are two or more structures of lowest energy which are equivalent by rotation about an axis or some other symmetry operation (see Figure 1.7).



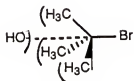
Figure 1.7: Symmetry Equivalence

6. Resonance contributors must have reasonable bondlengths and bond angles.

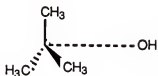
1.2.6 Steric Effects

Steric effects are important in determining at which position reaction will take place on a target molecule. They arise from repulsion between the electron densities of reactants [56JA2579], and are governed by Coulomb's law which states that the magnitude of a repulsion between two particles of like charge is inversely proportional to the distance

between them. An example of the determination of the region of attack on a target molecule by a reactant in a mechanistic step, by steric hindrance, is the hydrolysis of tert-butyl bromide, $(\text{CH}_3)_3\text{Br}$. This reaction does not take place by attack of hydroxide ion on the tert-butyl bromide molecule, because of the large steric hindrance between the CH_3 groups and the lone pairs on the oxygen atom (see Figure 1.8(a)), but takes place by formation of an ion pair of tert-butyl carbonium ion and bromide anion, and subsequent attack of the hydroxide anion on the carbonium cation [41F612] (see Figure 1.8(b)).



(a)



(b)

Figure 1.8: Steric Hindrance

1.2.7 Acidity and Basicity

The definition of acidity which will be used here is that given by Lewis [23MI142] in 1923: "a basic substance is one which has a lone pair of electrons which may be used to complete the stable group [octet] of one of its own atoms, and. . .an acid substance is one which can employ a lone pair from another molecule in completing the stable group [octet] of one of its own atoms." p-Nitroaniline (see Figure 1.9) is hence a stronger acid than aniline because the former can delocalize its lone pair on the amino nitrogen through the ring to the oxygens on the nitro group, on the grounds that oxygen is more electronegative than nitrogen [60MI296, 23MI139]. Since carbon is less electronegative than nitrogen, this "pull" is not felt in the aniline molecule, and while some delocalization does occur, the effect on acidity and other properties is not as great [60MI296]. Conversely, aniline is a stronger base than p-nitroaniline because its electrons in the lone pair on the amino nitrogen are less delocalized over the molecule and thus are more available for bonding.



Figure 1.9: Resonance Structures of p-Nitroaniline

1.2.8 Oxidation State

An oxidation occurs when electrons are taken away from an atom, and a reduction occurs when electrons are added to an atom. The method used to calculate whether or not an oxidation or reduction has taken place in the course of a reaction mechanism is to calculate the effective oxidation number by the "water addition method" [66JCE532] for the reactant and product and compare them. In this method, the degree of electron deficiency is assessed by a hypothetical series of hydrolyses (see Figure 1.10), both by addition and displacement, of multiple bonds and rings, until a saturated, open-chain structure is produced. If the oxidation number calculated by this method is greater for the product than the reactant, an oxidation

has taken place, and if the oxidation number for the reactant is greater than that for the product, a reduction has occurred. The rules for calculating effective oxidation numbers by the "water addition" procedure are as follows:

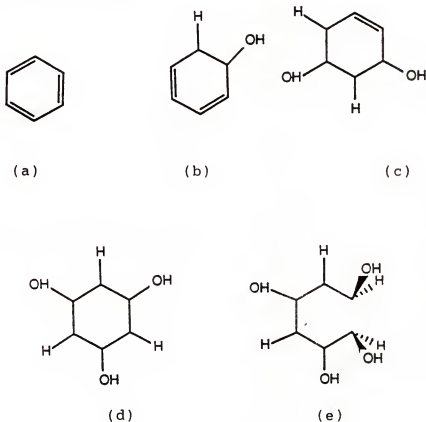


Figure 1.10: Oxidation Number Calculations

1. Add water molecules to all unsaturated areas on the compound: one for each double bond, two

for each triple bond, and one for each ring. In structures stabilized by resonance, one of the resonance contributors is chosen to undergo the hypothetical hydrolysis. For example, the benzene ring would have four water molecules added, three to hydrolyze the double bonds, and one to cleave the ring.

2. Find the number of atoms other than C and H present in the molecule. This number is the oxidation number for the compound.

In electron pushing to contrive projective mechanisms, inadvertent oxidation and/or reduction must be avoided; otherwise the law of charge conservation is violated.

1.2.9 Drawing the Mechanism

A series of reactants and products pictures are drawn, each showing the bonding situation and distribution of positive and negative charges (if any) in the reactant molecules. The Lewis bond structures of reactant(s) are drawn (substituting line bonds for electron-pair bonds).

Now arrows are drawn, in the reactants picture, placing the base of the arrow at the lone pair

(or bond) of the reactant molecule and pointing to the position on the second reactant molecule to which the electron pair "goes" during the course of the covalent bond-forming reaction.

For every electron pair which "goes" to a position on another reactant molecule, one pair of electrons must come away from that same position, in order to preserve the state of oxidation of that atom. The head of the arrow can also be drawn pointing to another position either within the same molecule, or to a position on another reactant molecule. In the two latter cases, a new covalent bond is formed from the base of the arrow to its head and is so drawn in the products picture. Formal charges must be calculated for each atom other than hydrogen in the molecule(s) and any positive or negatively charged atom must have its charge written above it.

The rule for movement of electron pairs, and thus the placement of the arrows, is that electron pairs move from a source to a sink, from positions of excess of charge to positions of scarcity of charge. Charge must be conserved in both reactants and products pictures. There must be equal numbers of positive and

negative charges present, so that both electroneutrality and charge conservation are observed.

1.2.10 Example: Formation of N,N-Dimethylbenzamide

A good example of the use of electron pushing in writing a mechanism is given by the formation of an amide, from an amine with a lone pair on its amino nitrogen atom and a compound which has a good "leaving group" on a carbon which is itself doubly bonded to an oxygen (a carbonyl carbon). A good "leaving group" is an anion or molecular fragment which can delocalize negative charge [87MI374, 79ACR198], (such as toluenesulfonate, -OTs, which is the conjugate base of toluenesulfonic acid, TsOH, 1) or an anion which attains noble gas configuration, such as chloride or bromide (Cl⁻ or Br⁻).

In the first reactants drawing, the reactant molecule, dimethylamine, HN(CH₃)₂, 2, (for structures, see Figure 1.11) and the substrate molecule, benzoyl chloride, C₆H₅COCl, 3, are drawn as shown in Figure 1.12(a). A lone pair is drawn above the amine nitrogen atom. An arrow is then drawn from this lone pair, which is the electron source, on the dimethylamine to the

carbonyl carbon of the benzoyl chloride molecule, and an arrow is drawn from the carbonyl carbon to above the carbonyl oxygen, which is the electron sink, in that it is more electronegative than the carbonyl carbon or amino nitrogen. In the first products drawing, Figure 1.12(b), the formal charges are drawn above the nitrogen and oxygen, one positive and one negative, respectively. A single bond is drawn from the amine nitrogen to the carbonyl carbon, and a single bond connects the carbonyl carbon and carbonyl oxygen. The products of this first reaction now become the reactants for the second reaction. The next reactants drawing is Figure 1.12(c): an arrow is drawn from the carbonyl oxygen, which serves as electron source, to the carbonyl carbon and an arrow is drawn from the carbonyl carbon to above the chlorine atom, which serves as the electron sink, since it is more electronegative than the oxygen. In addition, an arrow is drawn from the single bond attaching the hydrogen, a source of electrons since it attains noble gas configuration by losing an electron, to the amine nitrogen, which serves as the more electronegative sink, as shown. In the final products drawing (Figure 1.12(d)), the proton and chloride anion have their

formal charges drawn above them, the nitrogen atom has a lone pair drawn above it, and the double bond from the carbonyl oxygen to the carbonyl carbon has been restored in the product molecule, dimethylbenzamide, 4.

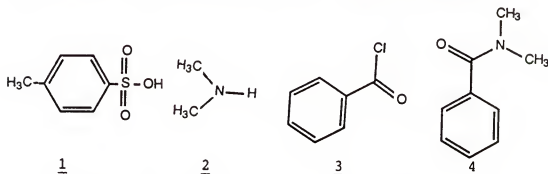


Figure 1.11: Structures of Compounds 1-4

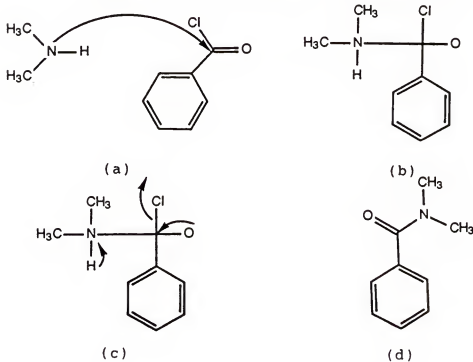


Figure 1.12: Reaction Mechanism

1.2.11 Limitations

For the most part, organic chemists are very successful in predicting the bonding of products using electron pushing, and other empirical models go far in predicting product stereochemistry. In some cases, however, these tools make ambiguous or incorrect predictions of the structure of the final product.

In the case of certain cycloaddition reactions the use of electron pushing can lead to an incorrect product structure. An example of an incorrect prediction given by "electron pushing" is that of the Diels-Alder reaction between cyclopentadiene, 5 and dimethyl fumarate, 6 (structures in Figure 1.13). A concerted electron pushing approach (see Figure 1.14) would predict that the least sterically crowded exo product 7 would be preferred, when in fact the more crowded endo product 8 is actually preferred, especially in the case of secondary orbital interactions between the diene and dienophile [72JA3633, 70JA7385] (See Figure 1.15).

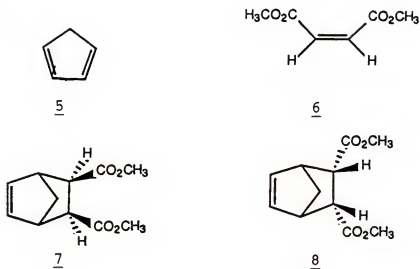
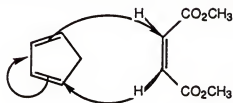
Figure 1.13: Structures of Compounds 5 - 8

Figure 1.14: Concerted Mechanism

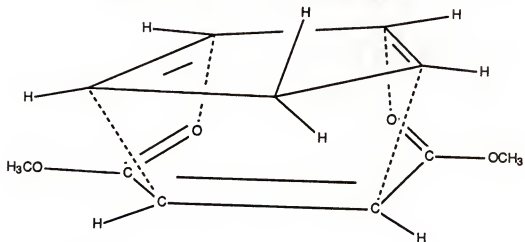


Figure 1.15: Secondary Orbital Interactions

In certain cases, the drawing of resonance contributors does not give the correct product. One of these cases is examined in greater detail in Chapter II. In brief, the experimentally observed nitration product for a series of N-phenyl substituted heterocyclic compounds was correctly predicted using resonance structures generated by electron pushing. N-phenylpyridinium was predicted, by the resonance structures produced by electron pushing, to react para to the pyridine ring substituent. In fact it was observed to react at the meta position.

1.2.12 Frontier Orbital Methods and Orbital Symmetry

In many cases, a reaction, for which electron pushing does not give correct results, can be explained by frontier orbital correlations, as proposed by Fukui [52JCP722, 54JCP1433], or by orbital symmetry correlations such as the Woodward-Hoffman rules [65JA2046, 65JA2511]. The orbitals on which these correlations depend are obtained via molecular orbital calculations using various kinds of theoretical formalism. In the previous example of the Diels-Alder

reaction of 5 and 6, use of a frontier orbital scheme (Figure 1.15) predicts the correct product [72JA3633, 70JA7385] and secondary orbital correlations between the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of the other give the correct orientation and structure. These qualitative molecular orbital methods have been of great use to organic chemists, and much has been done with the various methods.

1.3 General and Central Concept of the Present Work

The intent of the present work is to use various theoretical methods to attempt to explain, interpret, and rationalize assorted experimental results which appear to be counterintuitive and anomalous from the perspective of electron pushing, and to examine in some detail the mechanisms which underlie these results from a qualitatively theoretical point of view. The computational work took place in collaboration with theoretical workers from Professor Michael C. Zerner's group, and the experimental results to be investigated were obtained in the laboratory of Professor Alan R. Katritzky. The intention of the

author is not to devise or modify any existing theoretical method or formalism, which is why the present work is not termed "theoretical chemistry." Rather, existing theoretical techniques and computer codes are used to investigate and explain experimental results, hence the term "computational chemistry."

1.4 Brief Overview of Investigations Performed

Three different experiments were investigated and attempts were made in this work understand the results obtained using various computational methods. Also, the mechanism of stabilization of certain carbanions in which the carbanionic carbon was adjacent to a heteroatom with a positive formal charge was investigated.

In Chapter II, the problem studied was the nitration, on the phenyl ring, of a series of N-phenyl substituted heterocyclic systems. As mentioned previously, analysis of the resonance contributors and (for one of the molecules studied) examination of the effects of stabilization of a partial positive charge in a transition state by the lone pairs on an oxygen atom successfully predicted the position on the phenyl

ring at which nitration occurred, in all cases save for that of N-phenylpyridinium, which did not react at the expected position on the phenyl ring.

In Chapter III the investigation involved a reaction product, 9 (see Figure 1.16), which according to the Woodward-Hoffman rules could possibly have been aromatized, in an analogous manner to the aromatization of the cross-conjugated non-aromatic isomer of toluene 12, 2-exo-methylene-cyclohexa-1,4-diene 11, by a [1,5] sigmatropic shift of hydrogen, which should be suprafacial under thermal conditions [65JA2511]. The cross-conjugated compound 9 was thermally stable, however, and no aromatic product 10 could be formed from it, even under conditions of high heat and long reaction times.

In Chapter IV, the target of the investigation was the relative stability of saturated polycyclic compounds with fused six- and seven-membered rings. Usually a compound with three fused six-membered rings is considered to be more thermodynamically stable than its isomer with two seven-membered rings fused to a six-membered ring. In the case studied here, the product of a condensation reaction between hydrazine sulfate, formaldehyde, and hydrogen peroxide was not

the expected tricyclic product with fused six-membered rings, 13, but the "less stable" tricyclic compound with one central six-membered ring onto which two seven-membered rings were fused, 14 (see Figure 1.17).

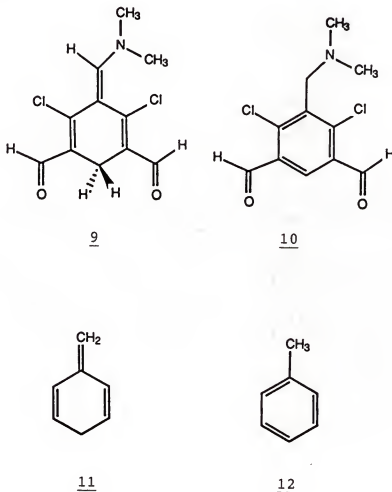
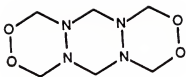
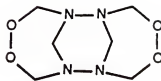


Figure 1.16: Structures of Compounds 9 - 12

1314Figure 1.17: Structures 13 - 14

In Chapter V, the mechanism of stabilization of carbanions which are adjacent to one or more heteroatoms having functional groups attached which give the heteroatom a formal positive charge, was studied. As there were no experimental results available with which to make direct comparisons, this part of the study was made from a more theoretical point of view, although suggestions for experimental measurements are made in the Chapter. The relative importance of dipole stabilization in these systems was

investigated, as well as certain other sources of stabilization. Predictions were made about the stability of various conformational isomers, as well as the ability of additional stabilizing groups to further stabilize the carbanion.

Finally, in Chapter VI, some general conclusions about the work in its entirety are made.

In the Appendix, the choice of the computational method used is explained, and some elementary details about the computational formalism and parameterization are given, as well as a summary of the parameters used for the lithiated compounds in Chapter V.

CHAPTER II
RATIONALIZATION OF A COUNTERINTUITIVE
RESULT IN AN
ELECTROPHILIC SUBSTITUTION REACTION

2.1 Introduction

2.1.1 Overview

Aromatic substitution by electron-deficient, positively charged electrophilic species is an important type of reaction in organic chemistry, and is used in preparing compounds which have many assorted uses, from aniline dyes to sulfa drugs. The character of functional groups already present on aromatic ring compounds determines the positions at which further electrophilic attack may take place. Usually, the directionality of attack may be predicted by "electron pushing", as described in the first chapter.

2.1.2 Directionality in Aromatic Substitution

Directionality describes the position on an aromatic ring where electrophilic attack is most likely to occur, based on the placement and electron-donating

or -withdrawing character of functional groups on the ring. The electron-donating or -withdrawing capability of a functional group is, for the most part, based on its electronegativity and ability to delocalize charge.

Generally, electrophilic attack occurs either ortho (depending on steric crowding) and para to a functional group, or attack occurs meta to the functional group (See Figure 2.1). Electron-donating groups, in putting excess electron density onto the aromatic ring, activate the ring towards electrophilic substitution and generally make attack at the ortho and para ring atoms preferable to attack at the meta ring atom (ortho, para activation) (See Figure 2.2). Electron-withdrawing groups usually deactivate the aromatic ring with regard to attack by electron-deficient species by lessening the electron density available for bonding in the ring. The smallest decrease takes place at the meta ring atom; hence that is where electrophilic attack takes place (meta activation) (See Figure 2.3).

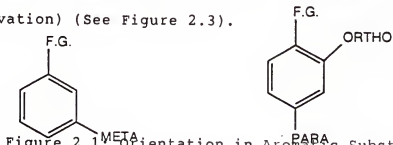


Figure 2.1: Orientation in Aromatic Substitution

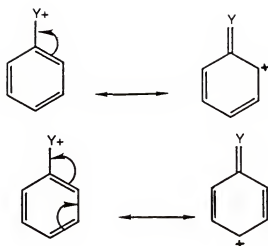


Figure 2.2: Ortho, Para Activation

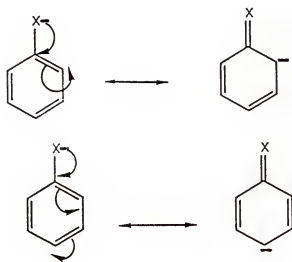


Figure 2.3: Meta Activation

2.1.3 Directionality by "Electron Pushing"

The directionality of attack in electrophilic aromatic substitution can usually be predicted by the heuristic method of "electron pushing" discussed in the first Chapter. In Figure 2.2 the directionality of attack by an electrophile on a ring substituted by an electron-donating group can also be shown by demonstrating the resonance stabilization (or lack thereof) of the transition state encountered during ortho, meta, and para attack. Some functional groups which donate electrons are shown on the figure. In Figure 2.3, the directionality of electrophilic attack on a ring substituted by an electron-withdrawing group can be shown in a manner analogous to the previous figure. Some functional groups which can cause meta substitution to occur are shown on the figure.

2.1.4 Electrophilic Substitution in Heteroaromatic Compounds: Nitration

According to the Katritzky and Rees in Comprehensive Heterocyclic Chemistry [86M1186], electrophilic attack at carbon atoms in aromatic

systems containing a pyridine-like nitrogen is an unfavored reaction. Nevertheless, it does occur, and the directionality of attack is highly dependent on the type of pyridine-like nitrogen present. Using "electron pushing" and transition state modeling, the products of electrophilic substitution can be predicted. Generally, in the case of unsubstituted pyridine, the attack takes place at the ring atom meta to the ring nitrogen (See Figure 2.4). The reaction occurs in acidic solution, and so the substrate is actually a pyridinium salt, with a formal positive charge on the ring nitrogen. The transition states for the ortho and para products can be drawn with two positive charges adjacent to one another. However, the transition state for the meta product has the two positive charges well separated, and one of them stabilized by a double bond. In the case of pyridinium N-oxides (See Figure 2.5), the site of attack is the para position, due to the electron-donating capability of the negatively charged oxygen atom. In the case of the nitration of unsubstituted pyrazole, the carbon ring atom most likely to be attacked is C-4. A competing reaction is electrophilic attack on the ring nitrogen in position 2 (See Figure 2.6).

2.1.5 Electrophilic Substitution on Phenyl Rings of N-Phenyl Substituted Heteroaromatics

The directionality of attack by electron-deficient species on the phenyl ring of N-phenyl substituted heterocycles can be predicted using the electron pushing technique and examining possible transition states. For compounds in which the substituted nitrogen on the heterocycle is written with a lone pair of electrons, the directionality of attack is predicted to be ortho (if there is a lack of steric crowding) and/or para. This is analogous to the directionality exhibited by N,N-dimethylaniline, or aniline itself, both of which compounds are strong ortho, para directors (See Figure 2.7). For compounds in which the substituted nitrogen on the heterocycle is written with a positive charge, it should be noted that these compounds are isoelectronic with the corresponding uncharged carbocyclic compound, i.e. with the positively charged nitrogen replaced by an uncharged carbon atom. When the electron pushing picture is drawn this way, the correct product can in many cases be predicted by looking at resonance structures or possible transition states.

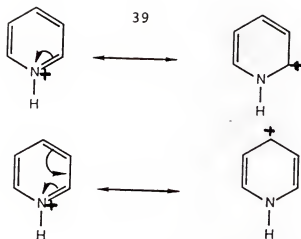


Figure 2.4: Substitution on Pyridine

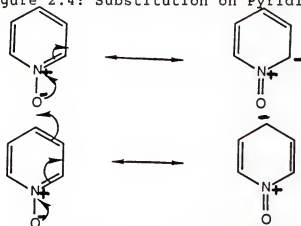


Figure 2.5: Substitution on Pyridine N-Oxide

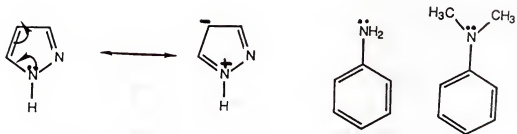


Figure 2.6: Pyrazole Substitution Figure 2.7: Anilines

2.2 Subject of the Present Work

2.2.1 Statement of Counterintuitive Results

A total of six compounds were studied (See Figure 2.8). Of these six, the resultant nitration product was predicted correctly in four cases by the electron pushing technique with incorrect results for two cases. The two compounds for which counterintuitive experimental results were obtained are N-phenylpyridinium [1893CB1925] and 1-phenyl-5-methyl-2-pyridone [61CA8440]. These compounds underwent nitration at the meta position, instead of the ortho or para position as predicted by electron pushing. In most cases, phenyl groups attached to a five- or six-membered ring containing nitrogen react at the para position, even if the reaction takes place on a cation.

2.2.2 Survey of the Literature

Phenyl rings attached to various pyrazoles [74J(P2)389], imidazoles [72J(P2)1654], 3-pyrazolone [75J(P2)1609], and 5-pyrazolones [73J(P2)1675] all nitrate at the para position. Even (3H)indolenium

reacts exclusively para to the attachment site of the nitrogen [64TL803]. The author has found no other record of any other previous work on the subject save for those papers mentioned above.

2.2.3 Experimental Work From This Laboratory

Experimental results from this laboratory, obtained by Dr. H. Faïd-Allah, indicate that N-phenylpyridinium reacts with an assortment of electrophiles, such as Br^+ , SO_3H^+ , and NO_2^+ , at the meta carbon. Thin layer chromatography (TLC) of crude product showed only one product to be formed. This product was shown to be the meta product by examination of ^{13}C chemical shifts on both phenyl and pyridinium rings.

The ^{13}C chemical shifts show a total loss of symmetry in the phenyl ring, which effectively rules out para product. Ortho product, which was considered unlikely to form due to the steric hindrance posed by the cyclic substituent on the phenyl ring, was ruled out by chemical shifts observed in the ^{13}C NMR spectrum.

2.3 Qualitative Theoretical Methods Used in Assessing Reactivity

Three methods are often used in assessing reactivity towards electrophilic substitution: The static method, in which electron densities in π orbitals are calculated and used in correlations which predict directionality of attack (a variant to this method uses partial charges on atoms instead of electrons in π orbitals); the transition state method, in which the geometry of a transition state is determined for each of the possible orientations of attack, the energy of each is calculated, and the correlation made by comparing transition state to ground state energies of reactants and products; and the frontier orbital method, which uses the orbital coefficients of the highest occupied molecular orbital to predict directionality of attack.

2.3.1 The Static Method

The static method was first proposed by Huckel in 1931 [31ZF312]. It postulates that the position most susceptible to attack by electrophilic reagents is that which has the highest calculated total π -electron

density. Many modifications to this method have been suggested, some of which are given in Dewar [46F764] and Longuet-Higgins [50JCP283]. A variation on this method used in this study is to calculate partial charges on atoms. Using this technique, the highest probability of attack by electron-deficient reagents is at the ring atom with the greatest partial charge.

2.3.2 The Transition State Method

The transition state method was first described in 1942 by Wheland [42JA900]. The principal assumption behind the method is that the differences in unsaturation energies of the hypothetical transition complexes can be used to predict the directionality of electrophilic attack. Results from this method have been widely reported [49J463, 52JA3355]. For the compounds studied here, this method is far too demanding from a computational standpoint, due both to the size of the molecules under consideration (and of the "supermolecule" which comprises the activated complex), and the slowness of the computational routine used in calculating transition state geometries.

2.3.3 The Frontier Orbital Method

The frontier orbital method was first presented by Fukui in 1952 [52JCP722]. It predicts that the position most likely to be attacked by an electrophile is that position which has the greatest electron density in the highest occupied molecular orbital in the ground state. This molecular orbital is equal to the square of the orbital coefficient (in conjugated systems, usually the p_z orbital) at the atom under consideration. This method is based on the assumption that in the vicinity of the transition state, electrons in both electrophile and reacting ring system will be delocalized and that transfer of electrons will occur between the ring system and the electrophile [54JCP1433]. The most important part of the electronic interaction in question is then assumed to be this transfer of electrons which may lower the energy of the activated complex. The electrons in the frontier orbitals are postulated to be most susceptible to this transfer. A pair of electrons are considered to be "frontier electrons" inasmuch as they are most closely related to the formation of a covalent σ -bond between electrophile and the π -electron system in the

ring. In the case of electrophilic substitution, this pair of electrons is supplied from the highest occupied molecular orbital in the π -electron system of the aromatic ring [52JCP722].

2.4 Aim and Objective of This Work

The objective of this study is to provide an explanation for an experimental result which is counterintuitive both from the standpoint of electron pushing and chemical experience. This result was briefly summarized above, in Section 2.2.1, and concerned the directionality of attack by electron-deficient reagents on N-phenylpyridinium. The expected orientation for the substitution product was para, but N-phenylpyridinium gave products which were meta-substituted. In order to provide an adequate and fairly general explanation for this experimental result, the geometries of five similar compounds (see Figure 2.8), namely N-phenyl-2-hydroxypyridinium 2, N-phenyl-4-hydroxypyridinium 3, N-phenylimidazolium 4, N-phenylpyrazolium 5, and N-methyl-(3H)indolenium 6, were optimized as was the geometry of N-phenylpyridinium 6, using the methods described in the Appendix. An

analysis was then made of the orbital coefficients and charges calculated, in order to determine any possible correlations which might give an insight into the counterintuitive directionality exhibited in the electrophilic substitution of N-phenylpyridinium.

2.5 Results of Calculations

2.5.1 MNDO Calculation Results

The coefficients of the p_z orbital of each of the phenyl ring atoms were calculated in the course of the geometry optimization of each N-phenyl substituted heterocyclic compound. These coefficients can be used as predictors of reactivity in electrophilic substitution reactions according to the frontier orbital scheme devised by Fukui [54JCP1433, 52JCP722]. In addition, partial charges, computed according to Dewar's scheme [77JA4899] were calculated for each atom in the phenyl rings. The coefficients and partial charges are given in Table 2.1. Using the frontier orbital method, the reaction is predicted to take place at the atom with the highest absolute value of the p_z coefficient. Simple Coulombic attraction [76MI417]

between electrophile and the phenyl ring atom with the most negative partial charge gives the predicted product expected by use of the static method.

Table 2.1: Reactivity Indices Obtained from MNDO Calculations: Coefficients of the p_z Orbital, and Partial Charges on Atoms (from optimized geometries)

<u>Compound</u>		<u>Ring Position</u>	
		<u>meta</u>	<u>para</u>
N-phenylpyridinium <u>1</u>	$C(p_z)$	0.477	0.002
	Charge	-0.033	-0.004
N-phenyl-2-hydroxypyridinium <u>2</u>	$C(p_z)$	0.480	0.000
	Charge	-0.041	-0.003
N-phenyl-4-hydroxypyridinium <u>3</u>	$C(p_z)$	0.479	-0.001
	Charge	-0.041	-0.001
N-phenyl-(3H)imidazolium <u>4</u>	$C(p_z)$	0.475	0.000
	Charge	-0.041	-0.001
N-phenyl-(2H)pyrazolium <u>5</u>	$C(p_z)$	0.48x	0.00x
	Charge	-0.04x	-0.00x
N-methyl-(3H)indolenium <u>6</u>	$C(p_z)$	0.477	-0.003
	Charge	-0.044	-0.007

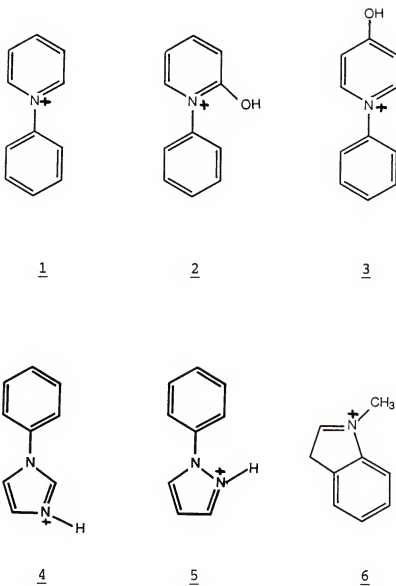


Figure 2.8: Structures of Molecules Studied

2.5.2 AM1 Calculation Results

The charges and p_z coefficients calculated using MNDO failed to predict reactivity correctly in the series of N-phenyl compounds 1 through 6. Since the geometries of the N-phenyl compounds 1 - 5 as optimized by the MNDO method had interannular torsion [dihedral] angles of nearly 90° , making the two connected rings nearly perpendicular to one another, the geometry optimizations were repeated on compounds 1 through 5 using the newer AM1 formalism and parameterization [85JA3902] which has been reported to yield optimized geometries closer to experimental results than MNDO. The AM1 formalism corrects for errors in MNDO, the most serious of which is a tendency for the core-core repulsions amongst atoms to be overestimated when the atoms are separated by a distance equal to the sum of their vanderWaals radii [85JA3903]. The core repulsion function in MNDO [77JA4899] was therefore altered to compensate for this. More details are given in the Appendix. One result of this modification, germane to the problem at hand, is that the resultant optimized geometries of the N-phenyl substituted heterocycles 1 - 5 each have interannular torsion [dihedral] angles in

the neighborhood of 45° . These values are closer to the interannular dihedral angle found for similar compounds by X-ray diffraction experiments. Partial charges on the atoms in the phenyl ring were calculated, as well as the p_z coefficients of the highest occupied molecular orbital, to serve as reactivity indices for electrophilic substitution reactions at sites on the phenyl ring [31ZP312,76MI417] as in the cases where data from MNDO calculations were used. The results are in Table 2.2 and the criteria for determining reaction site are the same as before.

2.5.3 Results of Single-Point RHF Calculations

In the case of the compound where movement about the bond to the sp^2 nitrogen was restricted, N-methyl-(3H)indolenium 6, the reactivity index from the coefficient of the p_z orbital, $C(p_z)$, calculated using AM1, predicted attack by the electron-deficient species to occur at the para position relative to the sp^2 nitrogen, where in fact reaction actually does take place [64TL803]. In the case of the compounds where rotation about the interannular axis is possible, compounds 1 through 5, no consistently correct set of

predictions could be obtained from the orbital coefficients or partial charges calculated by either MNDO or AM1. A technique for predicting orientation of electrophilic substitution in systems where the highest occupied molecular orbital and the next highest occupied molecular orbital are very close together in energy, and thus nearly degenerate, was given in the work published in 1954 by Fukui [54JCP1433]. In using this technique, calculations were performed with the interannular dihedral angle set at values of 0° (rings coplanar) and 90° (rings perpendicular to each other). It was noticed by this author that the symmetry of the highest occupied molecular orbital would switch with that of the next highest occupied molecular orbital in going from an interannular dihedral angle of 0° to an angle of 90° , and thus there would be a corresponding switch in the predicted orientation of attack by an electron-deficient species, from para to meta. It was decided to take a closer look at this phenomenon, and so a set of single-point restricted Hartree Fock (RHF) calculations were performed for each compound in which rotation about the interannular bond was possible. For each compound studied, the interannular dihedral angle was set to values 10° apart, starting at 0° and ending

at 90°. All other bond distances and angles were held constant, equal to those in the optimized geometry. The eigenvalues and eigenvectors for the p_z orbitals on the phenyl ring were then calculated, and are presented in the following tables, the eigenvectors in a symbolic form, expressed as a "Symmetry Type," which is more fully discussed in the Discussion Section.

Table 2.2: Reactivity Indices Obtained from AM1 Calculations: Coefficients of the p_z Orbital, and Partial Charges on Atoms (from optimized geometries)

<u>Compound</u>		<u>Ring Position</u>	
		<u>meta</u>	<u>para</u>
N-phenylpyridinium <u>1</u>	$C(p_z)$	-0.307	-0.550
	Charge	-0.105	-0.074
N-phenyl-2-hydroxypyridinium <u>2</u>	$C(p_z)$	-0.184	-0.531
	Charge	-0.108	-0.077
N-phenyl-4-hydroxypyridinium <u>3</u>	$C(p_z)$	-0.306	-0.531
	Charge	-0.105	-0.079
N-phenyl-(3H)imidazolium <u>4</u>	$C(p_z)$	-0.335	-0.543
	Charge	-0.103	-0.080
N-phenyl-(2H)pyrazolium <u>5</u>	$C(p_z)$	-0.278	-0.559
	Charge	-0.108	-0.072
N-methyl-(3H)indolenium <u>6</u>	$C(p_z)$	0.477	-0.003
	Charge	-0.044	-0.007

Table 2.3: Eigenvalues (energies) for Next Highest Occupied Molecular Orbitals and Highest Occupied Molecular Orbitals and their Symmetry Types for Certain Values of the Interannular Dihedral Angle for N-phenylpyridinium

	<u>Eigenvalue (a.u)</u>		<u>Symmetry Type</u>	
<u>Dihedral Angle</u>	<u>NHOMO</u>	<u>HOMO</u>	<u>NHOMO</u>	<u>HOMO</u>
0.000	-13.639	-13.410	A	B
10.000	-13.633	-13.416	A	B
20.000	-13.620	-13.431	A	B
30.000	-13.602	-13.455	A	B
40.000	-13.581	-13.486	A	B
46.6	-13.566	-13.509	A	B
50.000	-13.559	-13.521	A	B
60.000	-13.557	-13.538	B	A
70.000	-13.587	-13.521	B	A
80.000	-13.608	-13.510	B	A
90.000	-13.615	-13.506	B	A

Table 2.4: Eigenvalues (energies) for Next Highest Occupied Molecular Orbitals and Highest Occupied Molecular Orbitals and their Symmetry Types for Certain Values of the Interannular Dihedral Angle for N-phenyl-2-hydroxypyridinium

	<u>Eigenvalue (a.u.)</u>		<u>Symmetry Type</u>	
<u>Dihedral Angle</u>	<u>NHOMO</u>	<u>HOMO</u>	<u>NHOMO</u>	<u>HOMO</u>
0.000	-13.394	-13.184	A	B
10.000	-13.391	-13.189	A	B
20.000	-13.379	-13.201	A	B
30.000	-13.366	-13.223	A	B
40.000	-13.353	-13.256	A	B
50.000	-13.341	-13.295	A	B
51.06	-13.340	-13.300	A	B
60.000	-13.341	-13.324	B(?)	A
70.000	-13.375	-13.317	B	A
80.000	-13.401	-13.311	B	A
90.000	-13.411	-13.309	B	A

Table 2.5: Eigenvalues (energies) for Next Highest Occupied Molecular Orbitals and Highest Occupied Molecular Orbitals and their Symmetry Types for Certain Values of the Interannular Dihedral Angle for N-phenyl-4-hydroxypyridinium

	<u>Eigenvalue (a.u.)</u>		<u>Symmetry Type</u>	
<u>Dihedral Angle</u>	<u>NHOMO</u>	<u>HOMO</u>	<u>NHOMO</u>	<u>HOMO</u>
0.000	-13.543	-13.199	A	B
10.000	-13.539	-13.206	A	B
20.000	-13.527	-13.228	A	B
30.000	-13.510	-13.263	A	B
40.000	-13.491	-13.310	A	B
48.5	-13.475	-13.357	A	B
50.000	-13.472	-13.366	A	B
60.000	-13.453	-13.423	B	A
70.000	-13.477	-13.438	B	A
80.000	-13.514	-13.429	B	A
90.000	-13.527	-13.426	B	A

Table 2.6: Eigenvalues (energies) for Next Highest Occupied Molecular Orbitals and Highest Occupied Molecular Orbitals and their Symmetry Types for Certain Values of the Interannular Dihedral Angle for N-phenyl(3H)imidazolium

	<u>Eigenvalue (a.u.)</u>		<u>Symmetry Type</u>	
<u>Dihedral Angle</u>	<u>NHOMO</u>	<u>HOMO</u>	<u>NHOMO</u>	<u>HOMO</u>
0.000	-13.667	-13.253	A	B
10.000	-13.664	-13.262	A	B
20.000	-13.655	-13.290	A	B
30.000	-13.641	-13.335	A	B
40.000	-13.625	-13.396	A	B
41.37	-13.623	-13.406	A	B
50.000	-13.608	-13.469	A	B
60.000	-13.592	-13.548	A	B
70.000	-13.622	-13.578	B	A
80.000	-13.677	-13.569	B	A
90.000	-13.698	-13.566	B	A

Table 2.7: Eigenvalues (energies) for Next Highest Occupied Molecular Orbitals and Highest Occupied Molecular Orbitals and their Symmetry Types for Certain Values of the Interannular Dihedral Angle for N-phenyl-(2H)pyrazolium

	<u>Eigenvalue (a.u.)</u>		<u>Symmetry Type</u>	
<u>Dihedral Angle</u>	<u>NHOMO</u>	<u>HOMO</u>	<u>NHOMO</u>	<u>HOMO</u>
0.000	-13.711	-13.340	A	B
10.000	-13.708	-13.347	A	B
20.000	-13.700	-13.371	A	B
30.000	-13.686	-13.412	A	B
40.000	-13.670	-13.467	A	B
50.000	-13.652	-13.534	A	B
60.000	-13.635	-13.605	A	B
60.499	-13.635	-13.609	A	B
70.000	-13.674	-13.620	B	A
80.000	-13.726	-13.610	B	A
90.000	-13.748	-13.606	B	A

2.6 Discussion of Results

2.6.1 Discussion of MNDO Geometries

The results, using both the static method and the frontier orbital method, from the MNDO calculations do not serve to explain the experimentally observed differences in reactivity, since they predict that all of the compounds will undergo electrophilic attack at the meta position on the phenyl ring. This may be due to the fact that in the geometries optimized via MNDO, except in the case of the rigid (3H)indolenium ion, energetic minima were found corresponding to interannular angles approaching 90°, where the two rings of the system are nearly perpendicular to one another. It is probable that this is due to the tendency of MNDO to overestimate the magnitude of non-bonded repulsions [85JA3902]. The geometry for biphenyl, a similar system with a phenyl ring substituent on an aromatic (benzene) ring, has been experimentally determined, and the interannular angle between the two benzene rings is $22.5^\circ \pm 3.5^\circ$ by X-ray diffraction measurements [77CPL467]. The optimized

geometry of biphenyl, using the MNDO formalism and parameters, has an interannular angle of nearly 90° , which shows that the MNDO optimized geometries of the compounds studied are probably inaccurate by the same amount with regard to the interannular dihedral angle.

2.6.1.1 Discussion of MNDO orbital coefficients

The MNDO coefficients for the p_z orbitals (see Table 2.1) on the meta and para carbon atoms on the phenyl ring were calculated. The largest absolute values, which predict the orientation of reaction, were found for coefficients of p_z orbitals on the meta carbon atom in all cases studied. This result is correct for the two cases 1 and 3, but is incorrect for all of the other cases, so these coefficients are shown not to be an accurate predictor of reactivity for electrophilic substitution reactions involving ring systems 1 through 6.

2.6.1.2 Discussion of MNDO partial charges

Exactly the same observation can be made for the partial charges (see Table 2.1) as a predictor of

orientation. In each case, the largest partial charge lies on the meta carbon, so reaction would be expected to occur there. Partial charges as calculated by MNDO are not, therefore, an accurate predictor of orientation in the course of a reaction involving these compounds.

2.6.2 Calculation of Biphenyl Geometry

The geometry of biphenyl was calculated using AM1 in order to find out the magnitude of the interannular angle in order to gauge the quality of the AM1 parameterization as regards similar systems. The interannular angle at the energetic minimum was located at 36.3° , which corresponds favorably with the experimentally determined result of $22.5^\circ \pm 3.5^\circ$. From the geometries of the compounds optimized in this work, it is found that the interannular angles of similar compounds 1, 3, and 2 are within 5° of one another, N-phenylpyridinium at 46.6° , N-phenyl-4-hydroxypyridinium at 48.5° , and N-phenyl-2-hydroxypyridinium at 51.5° . The interannular angles of N-phenyl-(3H)imidazolium 4 and N-phenyl-(2H)pyrazolium 5 are not so close, as the angle for 5 is 61.0° , and the corresponding angle for 4

is 41.0° . Inasmuch as the main factor in increasing magnitudes of the interannular dihedral angle appears to be an increase of steric repulsion, the value of 61.0° for the interannular dihedral in 5 seems too large, and the value of 41° as seen in 4 seems more appropriate, especially in comparison with the pyridinium substituted systems and derivatives, which are more sterically bulky than imidazolium or pyrazolium substituted systems. Since the torsion between the two rings is very soft, and since it is difficult on a relatively flat potential surface to gauge the difference between local and absolute minima, it is suggested that the value of 61.0° for the magnitude of the interannular angle in 5 is not correct, and that the true value should be somewhere near 40° .

2.6.3 Discussion of AM1 Charges and Coefficients

The partial charges as calculated by AM1 predict (see Table 2.2) in all but two cases the incorrect product, so these are not a good predictor of reactivity in the electrophilic substitution of these

particular N-phenyl substituted heteroaromatic compounds, either.

The coefficients of the p_z orbitals from AM1 predict the correct result in 4 cases, amongst them (3H)indolenium and the para substituted compounds. The two cases where meta substitution was experimentally observed were incorrectly predicted to form para substitution product as well.

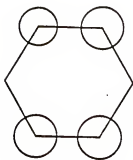
2.6.4 Discussion of Single-Point RHF Calculations

For each compound free to rotate about the interannular bond, a series of restricted Hartree Fock (RHF) calculations were done. In each series, all bond lengths and angles were held constant, equal to those in the optimized geometry, except for the interannular dihedral angle, which was varied over a range of 0° to 90°, in increments of 10°. This was done to determine more precisely where the shift in symmetry of the highest occupied molecular orbital took place (See Tables 2.3 - 2.7), and thus the change in predicted orientation of attack by electron-deficient species. The assumption made in all of these studies is that the geometries of the reactants near the transition state

closely resemble their geometries in the ground state, and so the ground state geometries provide a good estimate of the appearance of the transition state.

The orbital symmetries of the highest occupied molecular orbital and the next highest occupied molecular orbital were consistently of two types: Type A, in which there is a node (zero coefficient) for the p_z orbital at the para carbon on the phenyl ring, and Type B, in which there is no node for any p_z orbital for any of the phenyl ring carbons, but in which the coefficients at the para positions are much larger than those at the meta positions (See Figure 2.8).

Type A (meta)



Type B (para)

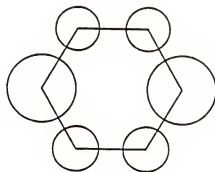


Figure 2.8: Symmetry Types for Phenyl Rings

The symmetry of the highest occupied molecular orbital in each case was observed to change at different points for each system studied into that of the next highest occupied molecular orbital, and vice versa. The energy eigenvalues associated with the two sets of eigenvectors were plotted against the values of the interannular angle, and connected by a smooth curve according to the symmetry type characteristic to the orbital. A curve was constructed from the energies of the molecular orbitals of symmetry type A plotted against values of the interannular dihedral angle, and the same was done with molecular orbitals of symmetry type B. These plots are in Figures 2.9 through 2.13.

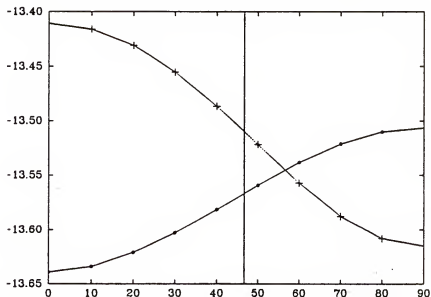


Figure 2.10: Plot of Eigenvalues vs. Dihedral Angle for N-phenylpyridinium

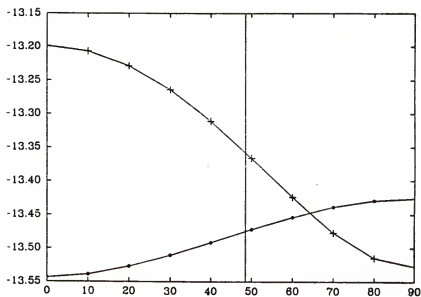


Figure 2.11: Plot of Eigenvalues vs. Dihedral Angle for N-phenylimidazolium

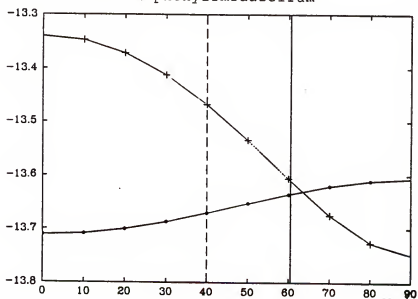


Figure 2.12: Plot of Eigenvalues vs. Dihedral Angle for N-phenylpyrazolium

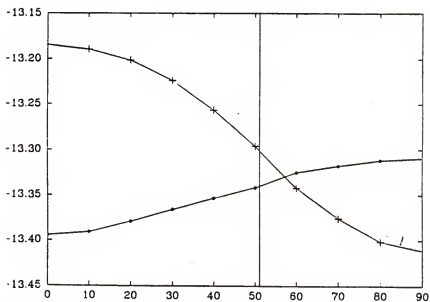


Figure 2.13: Plot of Eigenvalues vs. Dihedral Angle for N-phenyl-2-hydroxypyridinium

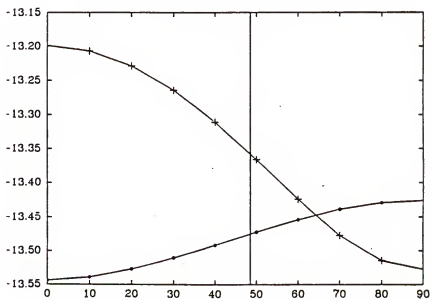


Figure 2.14: Plot of Eigenvalues vs. Dihedral Angle for N-phenyl-4-hydroxypyridinium

2.7 Conclusions

In conclusion, it has been shown that none of the usual predictors, such as partial charges on atoms or coefficients of the p_z orbital in the highest occupied molecular orbital of optimized geometries, give the correct result in the cases of electrophilic substitution studied.

It has also been shown that orientation of substitution can be correctly predicted using plots of energy eigenvalues plotted according to their symmetry versus increasing interannular dihedral angle, in the manner following:

1. In the cases where meta substitution was observed experimentally, the point of crossing of the two curves, and thus the point of symmetry switching of the highest and next highest molecular orbitals, was found to occur when the interannular dihedral angle was near 55° , but in the cases where para substitution was observed experimentally, the point of crossing was found to occur when the interannular dihedral angle was close to 65° .

2. In the cases where meta substitution was observed experimentally, the difference in dihedral angle between optimized geometry and crossing point was calculated to be between 6° and 9° , and in the cases where para substitution was experimentally observed, in all cases save for N-phenyl-(2H)pyrazolium (whose optimized interannular angle is anomalously large and may be due to inability of the algorithm used to distinguish between local and absolute minima on a relatively flat potential energy surface) it was calculated that the difference in dihedral angle between optimized geometry and crossing point is always greater than 15° .

CHAPTER III
COUNTERINTUITIVE FORMATION
OF A NON-AROMATIC
CONDENSATION PRODUCT

3.1 Introduction

3.1.1 Overview

Aromatic compounds are important substances and have many uses, from dyestuffs to medicinal drugs to plastics and so on. Aromatic compounds have been observed to be more stable, towards varying kinds of reagents, than their non-aromatic counterparts and they have a different sort of reactivity towards nucleophiles and electrophiles than is observed in non-aromatic compounds. Aromatic compounds generally undergo substitution reactions with electrophiles, rather than additions, because their aromatic stability is not lost when a substitution occurs. Compounds, such as dihydrobenzenes and dihydropyridines, which would be aromatic save for that they have two more hydrogens than the corresponding aromatic species tend to oxidize spontaneously in air to attain aromatic stabilization.

A sequence of reactions was performed in this laboratory in order to synthesize an aromatic (benzenoid) compound from cyclohexane-1,3-dione 1, phosphorus oxychloride 2, and dimethylformamide 3. The product of the reactions was not the expected aromatic compound, but instead a cross-conjugated isomer 4 (See Figure 3.1). The aromatic stabilization of the expected product was assumed to be so much greater than that of the cross-conjugated product actually formed that the formation of the actual product ran counter to chemical intuition and was considered to be anomalous.

In attempting to understand this result, the concept of aromaticity and its consequences, especially as regards aromatic stability, need to be further explored.

3.1.2 The Concept of Aromaticity

Badger has defined aromatic substances in the following way [69MI37]: "An unsaturated cyclic or polycyclic molecule or ion (or part of a molecule or ion) may be classified as aromatic if all of the annular atoms participate in a conjugated system, such that in the ground state, all the π -electrons (which

are derived from atomic orbitals having axial orientation to the ring) are accommodated in bonding molecular orbitals in a closed annular shell." This definition incorporates the definition of aromatic character made by Huckel in 1931 [31ZP312] in which aromatic species are planar cyclic compounds which have $(4n + 2)$ π -electrons, $n=0,1,2,3\dots$, which arises from calculations made of the energy levels of certain cyclic systems. It was found that those systems with rings of $p\pi$ atomic orbitals with 6, 10, 14... electrons in a closed shell are lower in energy (and thus more stable) than systems with rings of $p\pi$ atomic orbitals with 4, 8, 12... electrons in a closed shell.

The classical definition [69MI2] of an aromatic compound is based on the reactivity of that compound, as follows:

1. An aromatic compound will have more thermal stability than non-aromatic compounds, and will be more easily formed by pyrolytic methods.

2. Reagents such as nitric acid, sulfuric acid, and bromine will attack it under suitable conditions to give aromatically stabilized substitution products rather than addition products which have lost their aromatic stabilization.

3. The compound will be more resistant to oxidation by cold alkaline KMnO_4 or nitric acid, amongst others.

The predominating feature in all of the aspects of the classical definition of aromaticity is that aromatic compounds have an extra degree of stability over their non-aromatic counterparts.

3.1.3 Estimates of Degree of Aromatic Stabilization

The degree of aromatic stabilization exhibited by a compound is most often assessed by calculation of its empirical resonance energy, although other criteria, such as the ability to sustain an induced ring current [61J859] or the existence of characteristic absorptions in UV spectra [64MI1] are also used.

Empirical resonance energy values cannot be directly calculated, but must be estimated by analogy with other compounds. The most widely used [69MI44] method of calculating empirical resonance energy is based on heats of combustion. Bond contributions to the heat of combustion are obtained from a large collection of experimental results, and the contribution of each

bond type to the heat of combustion of the compound in question is summed. The heat of combustion of the corresponding non-conjugated molecule, or of the "contributing structure of lowest energy" for a conjugated molecule [69MI44] is obtained. The empirical resonance energy of a conjugated molecule is the difference of the actual heat of combustion of the molecule and the heat of combustion as calculated from the bond contributions data.

For example, benzene has a calculated heat of combustion of 825.1 Kcal/mol, 54.0 Kcal/mol for each of six single C-H bonds, 49.3 Kcal/mol for each of three single C-C bonds, and 117.7 Kcal/mol for each of three double C-C bonds, plus an additive factor of 1.0 Kcal/mol as a correction for a six-membered ring. The experimentally observed heat of combustion of benzene is 789.1 Kcal/mol, so the empirical resonance energy is equal to 36.0 Kcal/mol. An alternative method uses experimentally determined heats of hydrogenation [55MI1] instead of heats of combustion. Empirical resonance energies for monocyclic aromatic compounds are found to lie in the range of 15.8 Kcal/mol for furan, to 36.0 Kcal/mol for benzene.

3.1.4 Survey of Recent Work and Literature

Recent work in this laboratory, by Dr. C. Marson [85TL4715], has shown that in the condensation of the iminium salt of dimethyl formamide 1 and phosphorus oxychloride (see Figure 3.1 for structures), with cyclohexane-1,3-dione 2, the expected aromatic product, 2,4-dichloro-3-(N,N-dimethylaminomethyl)-benzene-1,5-dialdehyde 3, is not found. Instead, a non-aromatic tautomer, 2,4-dichloro-3-(dimethylamino-methylene)-1,4-cyclohexadiene-1,5-dicarboxaldehyde 4, is formed instead. This is a surprising result, in light of the fact that the resonance stabilization energy of benzene, ca. 36 kcal/mol [75MI217], as calculated in the preceding section, suggests that the predominant tautomer should be the benzenoid form and not the non-aromatic product found. Indeed, efforts by Marson to convert this non-aromatic tautomer into the aromatic form have not succeeded, each time resulting in formation of a tarry substance presumed to be the decomposition products of the starting material, or resulting in recovery of starting materials.

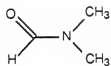
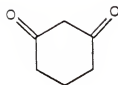
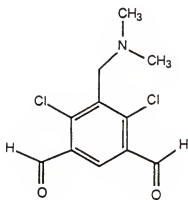
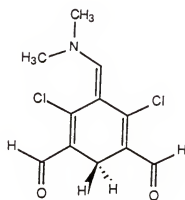
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Figure 3.1: Structures of Compounds Studied

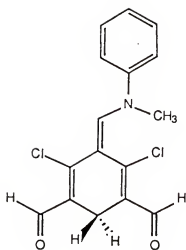
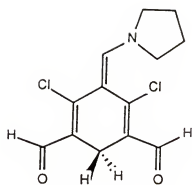
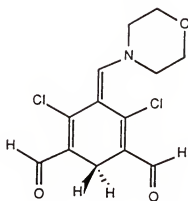
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Figure 3.2: Structures of Analogues

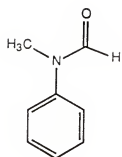
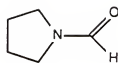
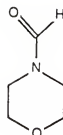
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Figure 3.3: Starting Materials for Analogues

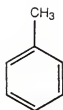
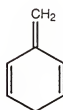
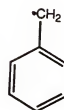
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Figure 3.4: Compounds for Barrier Study

3.1.5 Synthesis and Reactions of Analogues

A series of analogous 1,4-cyclohexadiene-1,5-dicarboxaldehydes 5a-c (See Figure 3.2), were synthesized in this laboratory by Dr. C. Marson from reaction of iminium salts of phosphorus oxychloride with N-methylformanilide 6a, pyrrolidine-N-carboxaldehyde 6b, and N-formylmorpholine 6c (See Figure 3.3), with cyclohexane-1,3-dione 2. The sole tautomer found in each case was the non-benzenoid form, from ^1H and ^{13}C NMR data. Efforts by Marson to convert the non-aromatic tautomer into the aromatic form failed, yielding either hydrolysis products, or a tarry residue containing neither the aromatic nor the non-aromatic tautomers. On addition of compound 4 to 36 M H_2SO_4 at room temperature, a deep purple solution was formed. ESR spectra made by Marson indicated the presence of radicals in this solution.

3.1.6 Synthesis of Benzenoid Isomer

The benzenoid form of compound 4 was formed by reaction of the iminium salt from phosphorus oxychloride and dimethyl formamide 1 with cyclohexane-

1,3-dione 2 at 100° C, in work performed by Dr. C. Marson in this laboratory; none of the non-aromatic form was detected, by either ^1H or ^{13}C NMR spectra.

The structures of compound 5b and its 2:1 adduct with hydroquinone, were confirmed by X-ray diffraction crystallography, performed by Drs. Palenik and Koziol in the Chemistry Department at the University of Florida. The geometries obtained by X-ray are given in the next section as a comparison with the geometries optimized by the author via MNDO.

3.1.7 Aim and Objective of This Work

The objective of this study is to attempt to provide a rationale for the exclusive formation of only one member of a tautomeric pair in each reaction above, and also to provide insight into the inability to convert from one tautomer to the other. These tasks were addressed by means of geometry optimization of the tautomers, calculation of their energies, and examination of a possible radical-like transition state (using an analogous compound), using the MNDO parameters and formalism contained in the standard program package MOPAC [77JA4899].

3.2 Results of Calculations

3.2.1 Methods Used

Full geometry optimizations were performed for compound 4, its analogue 5b for which an X-ray structure determination was performed (by Drs. Palenik and Koziol), and its benzenoid tautomer 3 using the MNDO parameters and formalism as described in the Appendix. The calculated bondlengths and bond angles of the optimized geometries are given in Tables 3.1 and 3.2 below, along with selected experimental X-ray values for 5b which serve as an indicator of the quality of the geometry optimization as compared with experimental data.

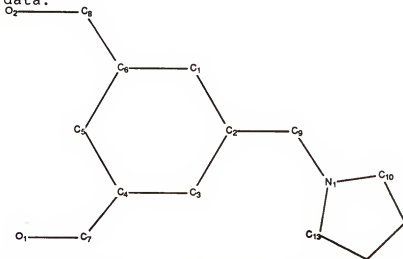


Figure 3.5: Numbering Scheme for 4 and 5b

Table 3.1: MNDO optimized bond lengths for 4 and 5b
and selected X-ray bond lengths for 5b

<u>Bond</u>	<u>MNDO Calculated Bond Lengths</u>		<u>X-Ray Bond Lengths</u>
	<u>4</u>	<u>5b</u>	<u>5b</u>
C1-C2	1.466	1.484	1.454(4)
C1-C6	1.365	1.359	1.349(3)
C2-C3	1.473	1.479	1.442(4)
C2-C9	1.393	1.369	1.388(3)
C3-C4	1.369	1.354	1.347(3)
C4-C5	1.491	1.519	1.495(5)
C4-C7	1.506	1.501	1.458(5)
C5-C6	1.489	1.503	1.495(4)
C6-C8	1.504	1.501	1.457(4)
C7-O1	1.217	1.219	1.214(4)
C8-O2	1.220	1.220	1.219(4)
C9-N1	1.373	1.410	1.323(3)
N1-C10	1.479	1.468	1.463(3)
N1-C13	1.482	1.469	1.480(3)

Table 3.2: MNDO optimized bond angles for 4 and 5b
and selected X-ray bond angles for 5b

<u>Angle</u>	<u>MNDO Bond Angles</u>		<u>X-Ray Bond Angles</u>
	<u>4</u>	<u>5b</u>	<u>5b</u>
C1-C2-C3	110.8	112.3	113.0(2)
C1-C6-C8	124.0	125.0	123.2(3)
C2-C9-N1	126.4	129.4	128.7(2)
C5-C4-C7	124.1	115.4	117.5(2)
C6-C5-C4	110.2	116.0	112.9(2)
C9-C2-C3	127.8	127.2	127.5(2)
C11-C1-C2	117.8	117.5	116.7(2)
C12-C3-C2	120.3	117.6	115.9(2)

3.2.2 Comparison of MNDO Results with X-ray Data

For the non-benzenoid systems 4 and 5b, there is good agreement with the experimental values for 5b, all of the experimental bond lengths lie within 0.01 to 0.05 Angstroms of the MNDO values with the MNDO values

usually the larger of the two. The sole exception to this is the bond length from the carbon of the exocyclic methylene to the nitrogen of the pyrrolidino substituent group in 4, which varies by 0.09 Angstrom, the MNDO bond length being the greater of the two. The calculated bond lengths and angles for the benzenoid tautomer 3 are, as expected, much different from those of its non-benzenoid form 4.

3.2.3 Calculation of Heat of Formation: Relative Stabilities of Products

The heats of formation of the compounds were also calculated. The value for the non-benzenoid tautomer is -26.3 Kcal/mol, which indicates that it is less stable than the benzenoid form, whose heat of formation is -39.7 Kcal/mol, by 13.4 Kcal/mol. This energy difference between the two forms is much less than the resonance energy of benzene, ca. 36 Kcal/mol [75MI217], which indicates that there is some degree of resonance stabilization in the non-benzenoid compounds, or some form of destabilization in the benzenoid forms.

3.2.4 Calculation of Transition State Energy

In order to get an idea of the size of the energetic difference between the ground state energies of the two tautomeric forms and a possible transition state, the energies of toluene 7, its non-benzenoid tautomer 3-(exo)methylene-1,4-cyclohexadiene 8, and benzyl radical 9 (See Figure 3.4), along with the energy of the hydrogen atom radical, were calculated. The unrestricted Hartree-Fock Hamiltonian option in the MOPAC program package was used, although the geometries of the radicals were not fully optimized. The existence of the radical-like transition state was based on the experimental result, obtained by Dr. C. Marson in this laboratory, given in the Introduction, in which reaction of non-aromatic tautomer 4 with 36 M sulfuric acid produced radicals, as shown by ESR spectral measurements.

3.2.5 Isodesmic Scheme for Benzyl Radical

The geometries of toluene and its non-benzenoid tautomer were optimized using the MNDO parameters and formalism as described in the Appendix.

The heat of formation of the benzyl radical was calculated using the optimized geometry of toluene, removing a hydrogen from the methyl group, and calculating the energy of the resultant benzyl radical using the unrestricted Hartree-Fock (open-shell) Hamiltonian as mentioned above.

The heat of formation of toluene was calculated to be 13.6 Kcal/mol, and the heat of formation of its tautomer 8 was found to be equal to 35.5 Kcal/mol. The energy difference between the two forms is 21.9 Kcal/mol in favor of the benzenoid form, which is still about 14 Kcal/mol less than the resonance energy of benzene, 36 Kcal/mol [75MI217]. The heat of formation of the benzyl radical was found to be equal to 52.3 Kcal/mol, and the heat of formation of the hydrogen atom radical was calculated to be 52.1 Kcal/mol. If these heats of formation are additive, the heat of formation of a transition state involving both of these radicals should be near 104 kcal/mol. The energy differences between the proposed transition state and the ground state of toluene 7 and its non-benzenoid tautomer 8 are 91.0 Kcal/mol and 70.0 Kcal/mol, respectively. These energy differences indicate that interconversion in this system is not

likely, if a radical-like transition state is involved. By analogy, interconversion between tautomers 3 and 4 is also considered to be unlikely, in accordance with experimental data, obtained by Dr. Marson in this laboratory.

3.3 Discussion of Results

The experimental data obtained by previous investigators in this laboratory [85TL4715] suggest that there is no easy route for interconversion of one tautomeric form into the other, for either tautomer. In the reactions where tautomers are formed, only one element of a tautomeric pair is formed, and conversion of that element into the other tautomer is seen to be not possible, insofar as none of the methods attempted were successful.

The calculations performed indicate that one tautomeric form is much more stable than the other, but the thermodynamically most stable tautomer, that having the lowest heat of formation, is not the tautomer produced in experiments at room temperature. Additionally, the magnitude of the energetic barrier between the two tautomers is, by analogy, estimated to

be very large (see Figure 3.4), close to 100 Kcal/mol, so the interconversion of tautomers is considered to be unlikely, especially if the activation energy for decomposition, polymerization, or some other competing reaction is less than this value.

Resonance stabilization does play some role in the stabilization of the non-benzenoid tautomer of toluene, 3-(exo)methylene-1,4-cyclohexadiene, but the energy difference between the two members of this tautomeric pair is only about 22 Kcal/mol, rather less than would be expected, in light of the fact that the resonance energy of benzene is 36 Kcal/mol. The energy difference between the two tautomers studied, 3 and 4, is 13 Kcal/mol, so the contribution of resonance stabilization to the stability of the non-benzenoid compound 4 is perhaps closer to around 10 Kcal/mol. There may be other factors at work here in the stabilization of this non-benzenoid tautomer, but the calculations performed do not readily suggest what they might be. Further calculations which take into consideration the role of solvent interactions with reactants and transition states should be performed, but are not at this time possible, due to a lack of suitable programs and/or computational resources.

3.4 Conclusions

The rationale for the experimental results suggested by these calculations is that the non-benzenoid product formed is a kinetic product, whose formation is determined by the relative energies of the transition state required to form it and the transition state required to form the benzenoid product, and thus the relative rates of formation of the non-aromatic and any other competing product. Due to the large amount of activation energy required for interconversion of tautomers, by analogy with the toluene - 3-(exo)-methylene-1,4-cyclohexadiene system, the equilibrium process required for tautomerization does not occur, so that the thermodynamically least stable product is the sole product formed by those reactions run at or near room temperature. In the case where the reaction is run at greater than 100° Centigrade, the energetics of the various transition states are assumed to be different, and so the more thermodynamically stable benzenoid product is formed.

CHAPTER IV
STRUCTURES AND ENERGIES OF SOME ISOMERIC
CONDENSATION PRODUCTS OF
HYDRAZINE, FORMALDEHYDE, AND HYDROGEN PEROXIDE

4.1 Introduction

4.1.1 Description of Procedure

Hydrazine sulfate reacts [21CB492] when dissolved in warmed hydrogen peroxide, with a mixture of warm formaldehyde and hydrogen peroxide to form, after a short time, a crystalline product. This product is allowed to accumulate for 1/2 hour, the mother liquor poured off, and the crystals washed successively with water, alcohol, and ether, and then dried in a desiccator over phosphorous pentoxide. The empirical formula for this product is $C_3H_6N_2O_2$, and the melting point is not reported, as the product explodes when heated. The product is light yellow in color, is insoluble in water, alcohol, ether, and ligroin, is somewhat more soluble in chloroform, nitrobenzene, and benzene, and is recrystallized from chloroform,

alcohol, or toluene, by heating strongly till product crystals are dissolved, then letting cool gradually.

4.1.2 History of Experimental Work

The molecular weight was reported by the original researchers as 102.1 g/mole, found by the cryoscopic method (freezing-point depression) using nitrobenzene as solvent. The structure of the product has been a point of controversy since it was first synthesized by von Girsewald and Siegens [21CB492] in 1920. The two researchers proposed a structure (Figure 4.1) consistent with the data available to them, on the basis of the reactivity of the compound with potassium iodide and its iodide derivatives thus formed, and on the basis of the reactivity of the compound with dilute hydrochloric and nitric acids. Titanium sulfate in dilute sulfuric acid reacted with the compound to give an orange color characteristic of peroxides, and more data were obtained using the results of the reaction with concentrated hydrochloric acid, Fehling's solution, and Ag/NH_3 in NH_3 solution.

No further work on the compound was published until 1960, when work by Prof. E. Schmitz [60A73]

showed that the molecular weight of the condensation product was actually twice that reported by the original investigators. Accordingly, by comparison with chemically similar compounds, and by qualitative analysis, a new structure for the condensation product was proposed (Figure 4.2).

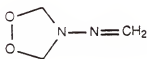


Figure 4.1: Siegens and von Girssewald Structure

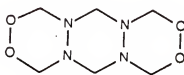
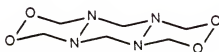


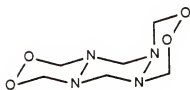
Figure 4.2: Schmitz Structure

Assuming that the structure given by Schmitz was correct, a conformational analysis of it was

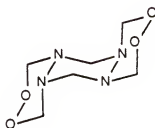
performed by Katritzky, Baker, Brito-Palma, Sullivan, and Finzel [79J(P2)1133] using ^1H and ^{13}C NMR. There are three possible conformational isomers for this system (Figure 4.3).



a



b



c

Figure 4.3: Conformers of Schmitz Structure

From the low-temperature NMR data cited, the "unexpectedly simple" spectra, consisting of one set of signals from the central ring methylene groups and three sets of signals from the methylene groups on the outer rings, was ascribed to an "accidental coincidence" of signals. This analysis, along with room-temperature NMR data, led to the conclusion that the structure for the condensation product was that given in Figure 4.3c, the mono-axial triequatorial conformer, in which two of the methylene quartets are thought to accidentally coincide.

In 1981, Dunitz and Seiler reported [81HCA000] an X-ray crystallographic structure determination of the compound first prepared by von Girsewald and Siegens. The structure found was tricyclic, but instead of three fused six-membered rings, the structure was found to consist of a central six-membered ring onto which were fused two seven-membered rings, as shown in Figure 4.4.

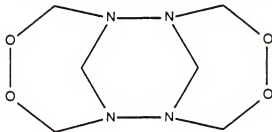


Figure 4.4: Dunitz and Seiler Structure

There are two possible conformational isomers for this system, one with S_2 (inversion) symmetry (Figure 4.5a), and one with C_2 (axis of rotation) symmetry (Figure 4.5b):

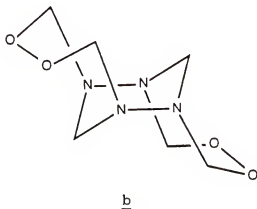
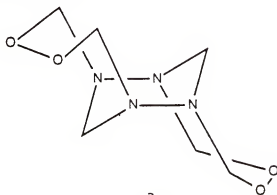


Figure 4.5: Conformers of Dunitz and Seiler Structure

The structure found in the X-ray is the S_2 conformer, and the NMR spectra for the compound were the same as reported by Katritzky et al.

The reason that this result is considered to be counterintuitive is that the strain energy of a seven-membered saturated carbocyclic ring is usually greater than the strain energy in a six-membered saturated carbocyclic ring. Studies have been made of the numerical value of this difference, and it was found that the seven-membered ring was 6.3 Kcal/mol less stable than the six-membered ring [65MI147]. In the six-membered ring, all of the bond angles are at their preferred value of 109.5° . In the case of a seven-membered ring, this is not so, and hence the energy of deformation of the bond angles from the value of 109.5° gives rise to the strain energy of the compound [65MI193]. These energetic trends would suggest that the system more likely to be formed is the one with three fused six-membered rings, not the system with two seven-membered rings fused onto a central six-membered ring.

4.2 Aim and Objectives of This Work

The objective of this study is to calculate the optimized geometries of conformers 4.3a-c and 4.5a-b and their heats of formation in order to provide an

estimate of the thermodynamic stability of the respective systems, and to indicate whether the product formation is controlled by kinetic or thermodynamic factors.

4.3 Results of Calculations

4.3.1 Methods of Calculations Used

Full geometry optimizations were performed for each of the five conformers mentioned above using the MOPAC package of programs as described in the Appendix. In three of the cases (4.3a, 4.5a, and 4.5b) there was enough symmetry present in the molecule to allow a symmetry constrained optimization to be performed, in which bond lengths, angles, and dihedral angles that were related to each other were set equal to each other in the optimization process, thus reducing the actual number of parameters to be calculated. The other two conformers (4.3b, 4.3c) had C_1 symmetry, and so a full geometry optimization with no symmetry constraints was required in those cases.

4.3.2 Results of Optimizations

The two latter geometries, 4.3b and 4.3c, failed to give optimized geometries. A small change in the coordinates at the final point reached produced a large change in the gradient calculated (the second derivative of the energy with respect to the molecular coordinates), and so the calculation was abandoned at that point. Small changes were made in the initial starting geometries, only to produce the same result. The cause for this result is unknown to this author, although it may rest with the parameterization. In work published in 1983 by Dunitz et al. [83JA7059], negative differential electron density was reported to occur between the peroxo oxygens in the outer rings, from an analysis of electron density maps obtained from an X-ray diffraction experiment. The parameterization may be trying to reproduce this and perhaps this is what causes the optimization to fail. However, for all but one of the geometries which were able to undergo a symmetry-constrained optimization, eventual optimization of the geometry did occur, after a long period of computation time (ca. 24 hours/compound, on a

DEC Microvax II). The energies for the optimized geometries are given in Table 4.1:

Table 4.1: Energies of Optimized Geometries of Tricyclic Dioxadiazacyclohexanes 4.3a-c and 4.5a-b (Energy in Kcal)

Conformer	Symmetry	Energy	Relative Energy	Remarks
4.3a	C _{2v}	37.9	0.0	optimized
4.3b	C ₁	38.8	0.9	optimized
4.3c	C ₁	---	---	not optimized
4.5a	S ₂	70.1	32.2	optimized
4.5b	C ₂	---	---	not optimized

4.3.3 Comparison of Experimental with Calculated Results

Contrary to the experimental results given by Dunitz and Seiler, this calculation predicts that the most likely conformer is 4.3a (in contrast to experiment which gives 4.5a as the only conformer), and that both of the conformers at the lower energy are nearly equal in stability. The energy of 4.3c is considered to be very close to that found for 4.3a and 4.3b, and the energy values for the two very similar

conformers 4.5a and 4.5b are considered to be close to each other as well, based on results for 4.3a and 4.3b.

4.3.3.1 Comparison of X-ray geometry with MNDO result

The geometry obtained from the X-ray analysis, which has S_2 symmetry, is compared with its optimized geometry from the MNDO calculation. Bond lengths of interest are given in Table 4.2, and bond angles of interest are given in Table 4.3.

Table 4.2 Comparison of Experimental and Calculated Bond Lengths for Tricyclic Compound 4.5a

<u>Bond</u>	<u>Bond Length (Angstroms)</u>	
	<u>MNDO</u>	<u>X-ray</u>
N-N	1.389	1.444
O-O	1.450	1.472
N-C(2)	1.474	1.468
N-C(1)	1.503	1.459 1.434
C(1)-O	1.445	1.428 1.445

Table 4.3 Comparison of Experimental and
Calculated Bond Angles for
Tricyclic Compound 4.5a

<u>Angle</u>	<u>Bond Angle (Degrees)</u>	
	<u>MNDO</u>	<u>X-ray</u>
N-C(2)-N	117.3	113.8
N-N-C(2)	116.7	112.6
N-N-C(1)	113.4	111.6
N-C(1)-O	108.8	111.5
C(1)-O-O	112.5	109.2

4.4 Discussion of Results

There are two reasons for the above results that immediately come to mind, in view of the experimental observations reported. One of them is that the product is produced under kinetic and not thermodynamic control, i.e. the initial product formed does not take part in a post-equilibrium process in order to attain the most thermodynamically stable geometry. In order to explore this further, the energies of the prospective transition states need to be determined, and the corresponding energy differences between transition state and product need to be calculated in order to estimate the relative rates of

formation of each type of product. The other possible reason concerns the peroxo O-O bond. Analysis of the experimental data indicated a negative differential electron density between the two atoms, and this may be reflected as an antibonding interaction in the theoretical calculations of energy and geometry.

4.5 Conclusions

Since the program failed to give optimized geometries for two of the conformers studied, and since the optimization of the other geometries was so laborious, there is some doubt as to the quality of the results, which contradict experimental evidence. Studies of similar monocyclic compound should be performed (perhaps using ab initio techniques) to assess whether or not sizable antibonding interactions exist across the O-O "bond", and if so, the parameters for the program package may have to be modified to account for this. Since the less thermodynamically stable product appears to be the only one formed, the energy of its precursor transition state needs to be found, and compared to the energies of the transition states in the formation of the other (hypothetically)

possible products. The program as it stands now is unable to be used for this type of calculation, due to the slowness of the routines used to calculate transition states, and also due in large part to the size of the system. The only conclusion that can be made at this point is that the product formed is produced under kinetic control.

CHAPTER V
FACTORS IN THE STABILIZATION OF CARBANIONS FROM
CYCLIC SECONDARY AMINES:
THE RELATIVE IMPORTANCE OF DIPOLE STABILIZATION

5.1 Introduction

5.1.1 Overview

Carbanions which are adjacent to a heteroatom bearing a formal positive charge are of wide use in synthetic organic chemistry. Some examples of carbanions in which at least one canonical form contains a heteroatom with a positive charge adjacent to a negatively charged carbon include: carboxamides {[69JO589], [65JA3365], [72JA9261], [73CJC1109], [73JA1628]}, a vinylogous carbox-sulfoxamide [73TL3379], isonitriles {[74ANE789], [73ANE323]}, imidates belonging to azaheteroaromatic systems {[68JO1087], [68JO1638]}, phosphoramides {[69BF1605], [73JMC41], [73JMC1], [74JO3042]}, isothiocyanates [72ANE933], azoxy compounds {[69TL2689], [73TL4701]}, nitrosoamines [75CB15], and azine 1-oxides [69JO1405].

The compounds studied above all had one adjacent positively charged heteroatom alpha to the carbanionic center. Very little was known about the effect on the stability of the carbanion of having two positively charged heteroatoms adjacent to the carbanionic center. In addition, there is some controversy over the source of the stabilization.

The controversy mentioned above centers around the mechanism of stabilization of these carbanions. Two possible sources of stability come to mind. The first is known as dipole stabilization, in which a functional group attached to a heteroatom adjacent to a carbanion induces a formal positive charge on that carbanion. The resultant dipole-dipole interaction, as shown in Figure 5.1, from work by Beak and Zajdel [84JA1014], stabilizes the carbanion. The second source of stability is the electrostatic attraction between an atom with a formal negative charge on the functional group attached to the heteroatom and the electropositive metal ion bonded to the carbanionic carbon, as in Figure 5.2. The calculations reported herein are an attempt to resolve which of these factors is more important in the stabilization of these carbanions.

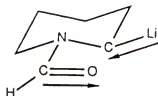


Figure 5.1: Dipole Stabilization

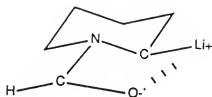


Figure 5.2: Electrostatic Attraction

5.2 Summary of Previous Work and Literature

Calculations have been performed on analogous compounds 1 and 2, which contain a single stabilizing group [81JO4108] (See Figure 5.3), using both ab initio

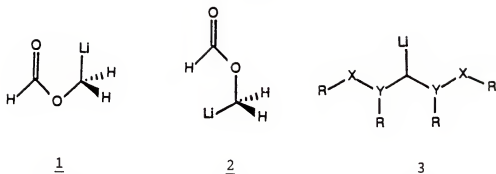


Figure 5.3: Stability: syn 1 versus anti 2

and semi-empirical techniques. The syn conformer 1 is found to be more stable than the anti conformer 2 by 13.2 kcal/mol, using geometries optimized via STO-3G basis sets and then calculating the energies using the split-valence 4-31G [80JA939] basis set. Although numerical results were not given, Bach et al. reported a trend using MNDO [77JA4899] similar to that reported using ab initio methods. The calculations reported on 1 and 2 using MNDO were repeated in this laboratory, with the result that the syn conformer 1 was found to be 19 kcal/mol more stable than the anti conformer.

5.3 Aim and Objective of This Work

In order to get a more quantitative insight into the mechanism of stabilization of the carbanions in which there are two positively charged nitrogens

adjacent to the carbanionic center, obtaining a quantitative estimate of the difference in relative stabilities between axial and equatorial diastereoisomers, and finding the difference in relative stabilization between compounds which have one stabilizing group and those which have two stabilizing groups, the geometries and energies of a series of compounds containing one and two heteroatoms adjacent to a carbanionic carbon in a saturated ring system were calculated, as well as geometries and energies of their neutral precursors.

5.4 Results of Calculations

5.4.1 Computational Method Used

The geometries of a series of carbanions with two adjacent heteroatoms each bearing a positive formal charge, 3 (See Figure 5.3), were fully optimized using the MNDO formalism and parameterization [77JA4899] contained in the MOPAC standard program package [85JA3907], as discussed in the Appendix, using parameters for lithium supplied by Prof. G. Ford [86MI1]. All energies given were reported relative to

the most stable conformer, whose stabilization energy was reported as 0 kcal/mol, and all bond lengths and interatomic distances were taken from the optimized geometries. The dihedral angles between the N-C-Li plane and the N-C=O plane were calculated using the standard vector result [84MI301]:

$$\cos \theta = \frac{\mathbf{a} \cdot \mathbf{b}}{|\mathbf{a}| |\mathbf{b}|}$$

where \mathbf{a} is a vector perpendicular to the plane N-C-Li defined by the coordinates of the amido nitrogen, lithiated carbon, and lithium atom, and \mathbf{b} is a vector perpendicular to the N-C=O plane defined by the coordinates of the amido nitrogen, carbonyl carbon, and carbonyl oxygen.

5.4.2 Enumeration of Conformers of Li Compounds

Lithiated 1,3-Diformylimidazolidine 4 can exist in three conformations: syn-syn (4a), syn-anti (4b), and anti-anti (4c) (See Figure 5.4). For lithiated 1,3-Diformylhexahydropyrimidine (5) (See Figures 5.5 and 5.6) there are a total of six possible conformations because each of the conformations

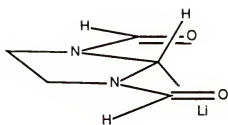
mentioned above can exist in two possible diastereomers with the lithium either axial (5a-c) or equatorial (5d-f), and for lithiated 1,3,5-Triformylhexahydro-sym-triazine (6) (See Figures 5.7 and 5.8), a set of eight conformations can exist, four of them with axial Li (6a-d), and four of them with equatorial Li (6e-h).

5.4.3 Results for Diformylimidazolidines

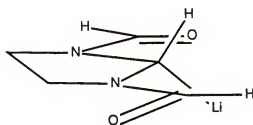
The results for the calculations on the diformylimidazolidines are given in Table 5.1:

Table 5.1: Calculated Relative Stabilization Energies and Selected Geometrical Parameters of 1,3-Diformylimidazolidines (4a-c).

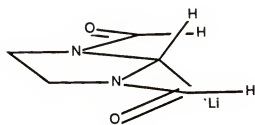
Conformer	Delta H ⁰ (Kcal)	Relative Delta H ⁰ (Kcal)	Dihedral Angle (degrees)	C-Li Bond (A)	O-Li Dist (A)
4a syn-syn	-90.2	0	38.0	1.97	2.18 2.19
4b syn-anti	-82.0	8	22.9	1.88	2.07 4.86
4c anti-anti	-61.8	28	47.6	1.91	4.47 4.49



4a

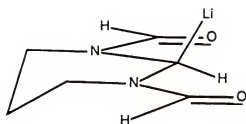


4b

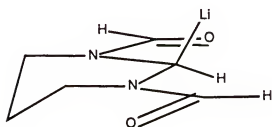


4c

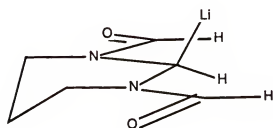
Figure 5.4: Imidazolidine Conformers



5a

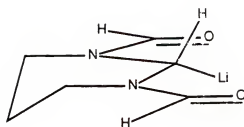


5b

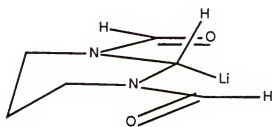


5c

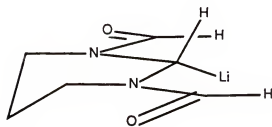
Figure 5.5: Hexahydropyrimidine Conformers (Axial)



5d



5e



5f

Figure 5.6: Hexahydropyrimidine Conformers (Equatorial)

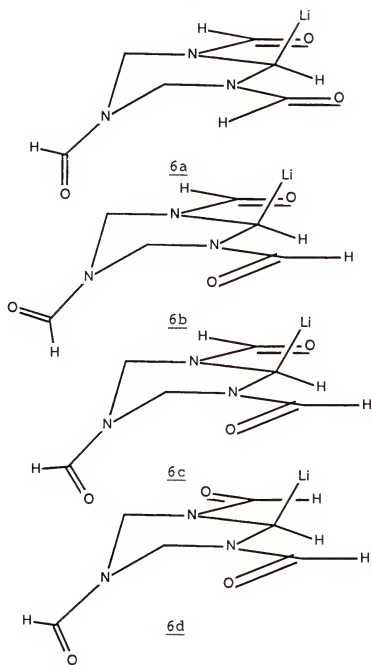


Figure 5.7: Hexahydro-sym-triazines (Axial)

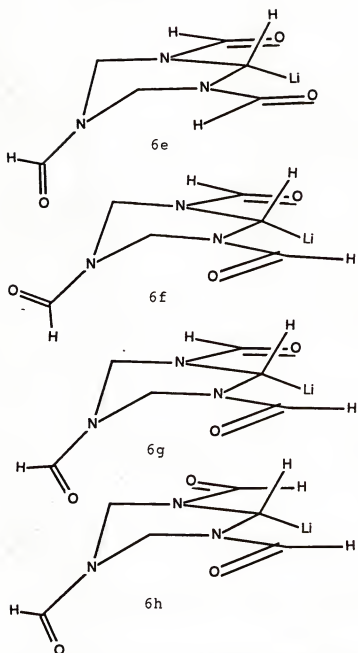


Figure 5.8: Hexahydro-sym-triazines (Equatorial)

Due to the near planarity of the five-membered imidazolidine ring, the N-C-Li plane makes angles with the N-C=O plane in the range of 23 to 48 degrees, angles which are intermediate between those calculated for the axial and equatorial conformers of the other compounds. The double O-Li coordination in the syn-syn conformer 4a makes it the most stable, followed by the syn-anti conformer 4b, in which there is one coordination between an oxygen and the lithium atom, and finally by the least stable anti-anti conformer 4c, in which there is no coordination between any oxygen and the lithium atom.

5.4.4 1,3-Diformylhexahydropyrimidine Results

The results of the calculations on the 1,3-Diformylhexahydropyrimidines are given in Table 5.2.

The calculations reveal that all of the conformers with equatorial Li are more stable than those with axial Li. The cause for this preference has been investigated previously by Bach et al. [83JO1509] and was attributed to orbital interactions; this matter will be discussed in greater detail in Section 5.5.1. The calculations were performed assuming a chair

Table 5.2: Calculated Relative Stabilization Energies and Selected Geometric Parameters of 1,3-Diformylhexahydropyrimidines (5a-f).

Conformer	Delta H ⁰ (Kcal)	Relative Delta H ⁰ (Kcal)	Dihedral Angle (degrees)	C-Li Bond (A)	O-Li Dist (A)	
Equatorial Lithium:						
5a syn-syn	-97.3	0	17.0	2.01	2.15	2.14
5b syn-anti	-84.5	13	9.0	1.98	2.07	4.22
5c anti-anti	-64.4	33	6.3	1.93	4.09	4.07
Axial Lithium:						
5d syn-syn	-55.6	42	110	1.94	4.66	4.63
5e syn-anti	-60.2	37	116	1.94	4.90	4.69
5f anti-anti	-61.7	36	117	1.94	4.93	4.88

conformation for the hexahydropyrimidine ring. The ring can also assume a twist-boat conformation. Calculations were carried out on these conformations as well. The same relative order of stability was found for the individual conformers, and so the results of those calculations are not reported here. Due to a lack of computer time, the energetic barrier for

interconversion from twist-boat to chair and vice versa was not studied. In the conformers with equatorial Li, the N-C-Li plane is nearly coplanar to that containing the N-CHO group, as shown in Table 5.2, and the conformers with axial Li have these planes bent slightly away from perpendicularity, perhaps also due to the orbital interactions referred to above. The lower stability of all of the axial conformers (5d-f) can also be attributed in part to the greater O-Li distances in these conformations.

Among the conformers with equatorial lithium, syn-syn (5a) is the most stable, as with the imidazolidines above. The increase in stability over the syn-anti (5b) conformer, 13 Kcal/mol, is very much less than that found going from anti-anti (5c) to syn-anti (5b), 20 Kcal/mol. The reverse order in stability is seen in the conformers with axial lithium, and the energy difference between the most and least stable conformer is in the neighborhood of a order of magnitude less than the energy difference between the most and least stable equatorially lithiated conformer.

5.4.5 Triformylhexahydro-sym-triazine Results

The results of the calculations on the 1,3,5-Triformylhexahydro-sym-triazines are given below:

Table 5.3: Calculated Relative Stabilization Energies and Selected Geometric Parameters of 1,3,5-Triformylhexahydro-sym-triazines (6a-h)

Conformer	Delta H ⁰ (Kcal)	Relative Delta H ⁰ (Kcal)	Dihedral Angle (degrees)	C-Li Bond (A)	O-Li Dist (A)
Equatorial Lithium:					
6a syn-syn	-115.2	0	16.3	2.01	2.17 2.15
6b syn-anti	-104.2	11	9.5	1.98	4.04 2.26
6c syn-anti	-101.8	13	9.9	1.98	4.23 2.08
6d anti-anti	-83.3	32	8.5	1.93	4.05 4.09
Axial Lithium:					
6e syn-syn	-73.8	41	74.7	1.92	4.26 4.76
6f syn-anti	-76.8	38	69.8	1.93	4.69 4.77
6g syn-anti	-78.3	37	70.4	1.93	4.22 4.72
6h anti-anti	-78.6	36	66.6	1.93	4.79 5.24

The results here are similar to those found for the diformylhexahydropyrimidines, in that all of the conformers where lithium is equatorial (6a-d) are more stable than any of the conformers where the lithium atom is axial (6e-h). In the former, the dihedral angle between the N-CHO plane and the N-C-Li plane is in the range of 9 to 16 degrees, which is nearly coplanar, and in the latter, the dihedral angle between the two planes is in the range of 67 to 74 degrees, which is closer to the perpendicular. Orbital interactions, as mentioned above for the diformylhexahydropyrimidines, probably play a role in the observed deviation from the perpendicular seen in the axial conformers.

Amongst the conformers with equatorial Li, the syn-syn conformer (6a) is the most stable. The next most stable conformers are the two syn-anti (6b, 6c) systems, whose difference in stabilization energy relative to both the syn-syn and anti-anti systems is almost identical to that found for the diformylhexahydropyrimidine conformers (5a-c). The difference in energy between the two syn-anti conformers may be due to the change in dipole-dipole interactions caused by the rotation of the 5-formyl

group. The opposite energetic trend is seen in the conformers with axial Li, with the syn-syn (6e) being least stable, the two syn-anti (6f, 6g) conformers intermediate in stability, and the anti-anti (6h) conformer most stable. The energy difference between the most and least stable axial and equatorial conformers is different by close to an order of magnitude, with the largest energy differences being seen in the conformers with equatorial Li, and small, but significant energy differences seen in the conformers with axial Li. The twist-boat conformer geometries and energies were also calculated. Since their relative order of stability was found to be the same as for the chair conformers, those results are not reported here. As above, due to a lack of computer time, the energetic barrier for interconversion between twist-boat and chair was not calculated.

5.4.6 Calculation of Electrostatic Interactions

It can be seen from the data in Tables 5.1, 5.2, and 5.3 above that a direct correlation exists between the stabilization of the equatorially lithiated species and the distance between the carbonyl oxygens

and the lithium atom. This suggests that electrostatic attractions play a large role in the stabilization of these species. Accordingly, the energy of these interactions were calculated using the distances and charges calculated by MNDO, using the approximate formula below [75MI46], where the charges on the lithium and oxygen atoms are taken to be equal in magnitude, at 0.5 charge units, and opposite in sign, and the factor of 80 is a conversion factor from Hartree atomic units to Kcal/mol which includes the charges as above.

$$E_c = -80 \left[\frac{1}{R(\text{Li} - \text{O}_1)} + \frac{1}{R(\text{Li} - \text{O}_2)} \right]$$

The results of this calculation, in units of Kcal/mole, and comparison with energies from the MNDO calculation, in units of Kcal/mole, are given in Table 5.4.

Table 5.4: Electrostatic Interaction Energies and Comparison with MNDO Calculated Energies (Kcal/mole) for (4a-c), (5a-f), and (6a-h)

Conformer	E_c (Kcal/mole)	MNDO Delta H°	
		Abs.	Rel.
4a syn-syn	-74	- 90.2	0.00
4b syn-anti	-55	- 82.0	8.20
4c anti-anti	-36	- 61.8	28.4

Table 5.4 - Continued

Conformer	E_c (Kcal/mole)	MNDO Delta H_o	
		Abs.	Rel.
Equatorial Li:			
5a syn-syn	-74	- 97.3	0.00
5b syn-anti	-58	- 84.5	12.8
5c anti-anti	-39	- 64.4	32.9
Axial Li:			
5d syn-syn	-34	- 55.6	41.7
5e syn-anti	-34	- 60.2	37.1
5f anti-anti	-33	- 61.7	35.6
Equatorial Li:			
6a syn-syn	-74	- 115.2	0.00
6b syn-anti	-58	- 104.2	11.0
6c syn-anti	-55	- 101.8	13.4
6d anti-anti	-39	- 83.3	31.9
Axial Li:			
6e syn-syn	-36	- 73.8	41.4
6f syn-anti	-34	- 76.8	38.4
6g syn-anti	-36	- 78.3	36.9
6h anti-anti	-32	- 78.6	36.6

It can be seen from these results that there is a good correlation between the energy differences for the equatorially substituted conformers 4a-c, 5a-c, and 6a-d, calculated both from MNDO and the electrostatic formula given above. This correlation does not exist for the axially lithiated conformers 5d-f and 6e-h. The energy differences arising here must be therefore be from a different source.

5.4.7 Correlation of Dihedral Angle and Energy

The primary source of stabilization in the equatorial lithiated conformers is probably a combination of Coulombic and charge-dipole interactions. In looking at the energy values for the various axially substituted lithiated compounds, an interesting relationship between the MNDO calculated energy and the dihedral angle that the C-Li bond makes with the plane of the N-formyl group becomes quite apparent. In terms of Coulombic attraction between the Li and the two oxygen atoms, the expectation is that the stabilization energy will increase as this dihedral angle decreases, but at a relatively small rate, since Coulombic attraction decreases as the inverse of the

distance. Instead, a dramatic increase in stabilization is seen as the dihedral angle comes away from perpendicularity:

Table 5.5 Dihedral Angle in Conformers with Axial Li Compared with Their MNDO Energies

Conformer	Dihedral Angle		MNDO Energy	
			Abs.	Rel.
<u>5d</u>	110	7.0	-55.6	6.1
<u>5e</u>	116	1.0	-60.2	1.5
<u>5f</u>	117	0.0	-61.7	0.0
<u>6e</u>	75	8.0	-73.8	4.8
<u>6f</u>	70	3.0	-76.8	1.8
<u>6g</u>	70	3.0	-78.3	0.3
<u>6h</u>	67	0.0	-78.6	0.0

From the data above, it seems that as the dihedral angle approaches 90° , the energy increases by about 1.0 to 1.5 Kcal/mole per degree. When the dihedral angle between the two planes is equal to 90° , the maximal orbital interaction between the amide π -system and the filled p-orbital on the carbanionic carbon is made possible. Since this interaction is strongly destabilizing, as discussed in the Discussion of Results section (see below), the closer the dihedral angle comes to 90° , the less stable the conformer should be. This is indeed as it is found from MNDO, and

so the energetic ordering of the conformers with axial Li is most probably due to destabilizing orbital interactions.

5.4.8 Energetics of Lithiated Carbanion Generation

The results above only concern the conformational stability of the lithiated carbanionic species. In order to gauge the effect of stabilization by first one, and then two, N-CHO groups on the energetics of carbanion formation, the energy of the carbanion generated from cyclohexane (no N-CHO stabilizing group) was compared to that of the carbanions generated from N-formylpiperidine (one N-CHO stabilizing group) and 1,3-diformylhexahydro-pyrimidine (two N-CHO stabilizing groups). The energetics of the transformation from "naked" carbanion to lithiated species were also studied, and the results are given in Tables 5.6 and 5.7. In all cases, the geometries of all compounds involved were optimized, and SCF energies were calculated, using the MNDO parameters and formalism [77JA4899] as found in the MOPAC standard program package [85JA3907].

Table 5.6: Energetics of "Naked" Carbanion Generation in Compounds with One and Two N-CHO Stabilizing Groups as Compared to Unstabilized Compounds.



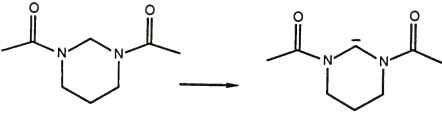
Reaction	Energy
 <chem>C1CCCCC1 >> [C-]1CCCCC1</chem>	$+ H^+$ <hr/> 28 Kcal/mol
 <chem>CC(=O)N1CCCCC1 >> CC(=O)[N-]1CCCCC1</chem>	$+ H^+$ <hr/> 23 Kcal/mol
 <chem>CC(=O)N1CCN(CC1)C(=O)C >> CC(=O)[N-]1CCN(CC1)C(=O)C</chem>	$+ H^+$ <hr/> 8 Kcal/mol

Table 5.7: Energetics of Lithiated Carbanion Generation in Compounds with One and Two N-CHO Stabilizing Groups as Compared to Unstabilized Compounds.

Reaction	Energy
$\text{Li}^+ + \text{Cyclohexyl}^- \longrightarrow \text{Lithiated Cyclohexane}$	-25 Kcal/mol
$\text{Li}^+ + \text{N-(formyl)cyclohexyl}^- \longrightarrow \text{Lithiated N-(formyl)cyclohexane}$	-37 Kcal/mol
$\text{Li}^+ + \text{N,N-bis(formyl)cyclohexyl}^- \longrightarrow \text{Lithiated N,N-bis(formyl)cyclohexane}$	-59 Kcal/mol

These results suggest that carbanion formation in the presence of two stabilizing groups is very much easier than that where only one stabilizing group is present, and that the formation of lithiated compound where two stabilizing groups are present is energetically favored in the extreme.

5.5 Discussion of Results

In the discussion of the stabilization of the carbanions considered in this work, it comes to mind that the word "stabilization" is used rather loosely. Stabilization can mean decreased reactivity of the lithiated compound towards other like molecules, leading to less likelihood that the carbanion formed will self-condense, or it can refer to the various possible conformers arising from the rotation of the acyl groups, or it can refer to the preference for equatorial lithiation over axial lithiation. In this section, all three of the above topics will be discussed, and a possible mechanism for the reaction which accounts for self-condensation as well as product formation will be proposed.

5.5.1 Equatorial Lithiation vs. Axial Lithiation

In all of the calculations reported above, there was a distinct energetic preference for equatorial lithiation over axial lithiation. Bach et al. [83JO1509] performed ab initio calculations on a series of carbanions which had a positively charged heteroatom alpha to the carbanionic center. In these calculations on the "naked" anion, there was a pronounced preference for the anion to take up the anti coplanar configuration, where the lone pair of the carbanion was coplanar with the N-formyl group, and the syn configuration was at higher energy (See Figure 5.3). This preference was attributed to the fact that the dipole-dipole interaction energy between the carbonyl dipole and the dipole consisting of the carbanionic carbon and the alpha heteroatom (in this case, N) in the anti configuration was less than that in the syn configuration. In the system with Li present, the opposite order of energies was obtained, syn more stable than anti, and this was explained by the strong electrostatic attraction between the Li cation, the carbanionic carbon, and the carbonyl

oxygen, which carries a rather large partial negative charge. Moreover, the energy and orbitals of the configuration with the lone pair of the carbanion normal to the plane of the N-formyl group were calculated. It was found that this configuration was even less stable than any of the coplanar configurations. The authors of that paper performed a study using the fragment orbital approach, and found that the axial carbanion orbitals bore a strong similarity to those found in the butadiene anion, which, since both of the anti-bonding orbitals are filled as well as both of the bonding orbitals, is strongly destabilized. In the coplanar configurations, there was no such destabilizing interaction, and so the coplanar configurations, corresponding to equatorial lithiation, were found to be more stable than the configurations where the carbanionic lone pair was normal to the N-formyl group. In the compounds in this study, both of the syn and anti conformations are available for the formation of "naked" anions, due to the ability of the carbonyl group to rotate about the N-CHO bond. The orbitals of the anions corresponding to both the equatorial and axial configurations of the anti,anti conformer of 1,3-diformylhexahydropyrimidine

were calculated. These results are similar to those found by Bach et al., and show that the major factor in the preference of equatorial lithiation over axial lithiation is a destabilizing orbital interaction.

5.5.2 Conformational Preferences

The conformational preferences found throughout all of the various cyclic compounds studied, the 1,3-diformylimidazolidines 4a-c, the 1,3-diformylhexahydro-pyrimidines 5a-f, and the 1,3,5-triformylhexahydro-sym-tri-azines 6a-h, can all be explained by the effects of the electrostatic interaction between the Li cation and the carbonyl groups. Both Coulombic attraction and charge-dipole interaction play a role in the stabilization of the most stable conformers (syn,syn and syn,anti) relative to that found for the least stable anti,anti conformers, in which these interactions are negated due to the large distance between the cation and the carbonyl groups and oxygens. The most significant role is played by simple Coulombic interaction, which is an order of magnitude greater in strength than the charge-dipole interactions, which only have a limited effect

on stabilities. Dipole-dipole interactions do not play a significant role in the stabilization of the various conformers due to the distances involved; there is a factor of $1/r^3$ in dipole-dipole interactions, as opposed to $1/r^2$ for charge-dipole interactions, and $1/r$ for Coulombic interactions, so there is a distinct dependence on distance from the cation for these various types of interactions.

5.5.3 Reactivity of Stabilized vs. Non-Stabilized Systems

The substitution of one N-formyl group for a methylene group in a cyclic saturated compound, such as cyclohexane 7, to form a product such as 8, greatly increases the ability of the resultant product to form a carbanion on treatment with a metallating reagent, such as lithium diisopropylamide (LDA) or tert-butyllithium(t-BuLi). The decrease in energy of the N-CHO stabilized carbanion relative to the cyclohexyl carbanion is close to 15 Kcal/mole, so the stabilization of the mono-stabilized "naked" anion is about 15 Kcal/mole, from the calculations reported above, for compounds 7 - 8. The substitution of a second N-formyl group for the $-CH_2-$ group on the

opposite side of the carbanionic carbon might be expected to increase the stabilization of the resultant carbanion 9 by about the same degree, so that the stabilization of bi-stabilized carbanion 9 is 30 Kcal/mole relative to cyclohexyl anion. This is not observed. Instead, the increase in stabilization is only 5 Kcal/mole in the "naked" carbanion, which is 20 Kcal/mole more stable than 8, 10 Kcal/mole less than expected.

When the lithium cation is introduced, so that the compounds formed are lithiated carbanions 10 - 12, the increase in stability on going from cyclohexyllithium 10 to N-formylpiperidinyl lithium 11 is 37 Kcal/mole. The increase in stability on going from a mono-stabilized syn system 11 to a bi-stabilized syn,syn system 12 is 22 Kcal/mole, which is almost 2/3 of that expected. This increase can be explained simply by considering that in a mono-stabilized system, the cation can get much closer to both the oxygen and carbanionic carbon than in the bi-stabilized system, in which the cation is equidistant between the two carbonyl oxygens. The correspondence between the results obtained for the Coulombic attraction energy for the syn,syn and syn,anti systems 5a and 5b and the

results for the bi- and mono-stabilized systems mentioned above gives additional evidence for this kind of distance effect.

5.5.4 Relative Importance of Dipole Stabilization

As discussed above, dipole stabilization of a carbanion exists when a formal positive charge is induced on a heteroatom adjacent to the carbanionic center. Dipole stabilization involves a canonical structure in which the carbonyl double bond becomes a single bond, with the carbonyl oxygen possessing a formal negative charge. This structure predicts two events in the molecule, first a lengthening in the C-O bond from a double-bond value (near 1.22 Angstrom) to a single bond value (near 1.34 Angstrom), and second, a marked increase in negative charge on the oxygen. Carbon atoms adjacent to such a nitrogen are expected have more carbanionic character, i.e. to have a greater partial negative charge, than carbons which lack this kind of stabilization. In the geometry optimizations performed, in no case did the carbon - oxygen bond length exceed 1.25 Angstrom. The partial negative charges on the oxygen atoms were seen to increase as

distance from the lithium atom decreased. The dipole stabilization model as described herein is therefore not useful, as the canonical structure on which it depends is the same, whether the C-O group is pointing in the same direction as the C-Li bond, or if the C-O group is pointing away from the C-Li bond. In either case, the change in charge on the oxygen atom would be expected to be the same, and this is not seen. Thus dipole stabilization is not useful in describing the stabilization of these carbanions. Electrostatic attraction energies have been calculated and are included in the Tables above. Good correlations are seen between them and the energies of the various conformers, and so it can be concluded that chelation of Li by electrostatic attractions between it and the atoms with partial negative charges in the neighborhood is responsible for the stabilization trends seen in these compounds.

5.6 Conclusions

The basis for stabilization of the carbanions studied can be concluded to be an electrostatic attraction between the electropositive lithium ion and

the carbanionic center and negatively charged carbonyl oxygens, from the results of the calculations given above. The most stable conformer is the syn, syn equatorially lithiated conformer, and the compounds with two stabilizing groups are predicted to be much more stable than those with one stabilizing group. The amount of stabilization gained with two "stabilizing groups" is predicted to be very much more than that gained with only one "stabilizing group".

Some experimental evidence would be useful in looking at the various possible types of stabilization of these carbanions. This author has only seen one sort of experimental evidence quoted to support dipole stabilization, namely, yields of "trapped" carbanionic products. This evidence cannot serve as an assay of quantity of carbanion formed, as in most cases, only the percentage of "trapped" carbanionic product is given, and no other breakdown of product yields is given. The reason that this sort of evidence is not usable is that carbanions once formed may decompose, polymerize, or reform starting materials. No product breakdown can thus give any indication of the relative stability of a carbanion, or even of its tendency to self-condense, since decomposition or further reaction

with other materials present in the reaction mixture may consume self-condensed carbanions. There are, however, methods of providing experimental verification for the calculations above. One way is to do conformational studies using NMR spectroscopy, and using dynamic NMR, to calculate the energy barriers for interconversion between the (anti, anti), (syn, anti), and (syn, syn) conformers. Another method that can be used to provide experimental confirmation is to use the energies calculated by way of the isodesmic schemes. The isodesmic schemes presented above can be utilized in the prediction of pK_a values, using the standard equation:

$$\Delta G = -RT \ln K_a$$

where the energy differences calculated are equated to the ΔG for the equation.

In order to provide a much needed experimental comparison, the values for the experimental pK_a 's need to be determined.

CHAPTER VI

GENERAL CONCLUSIONS

The intent of this research was to examine several diverse problems encountered in the synthesis or reactions of certain kinds of heterocyclic molecules by way of a computational method widely available to organic chemists, which would run on a microcomputer affordable to most organic chemists, and take a reasonable amount (<24 hours) of computer time per calculation.

The computational method chosen was AM1/MNDO, written by M. J. S. Dewar, G. P. Ford, W. Thiel, and J. J. P. Stewart. This method uses semi-empirical formalism and parameters designed to reproduce geometries and heats of formation, and is available through the Quantum Chemistry Program Exchange at the University of Indiana in Bloomington.

The quality of results, with regard to their applicability towards providing insight into

experimental results, obtained in the course of the investigation varied from fair, in the case of the tricyclic saturated heterocyclic condensation products of hydrazine sulfate, formaldehyde, and hydrogen peroxide, to good, in the case of the counterintuitive orientation of nitration of certain N-phenyl-substituted heteroaromatic compounds.

In the case of the N-phenyl-substituted heteroaromatic compounds, the correlation obtained between the symmetry of the phenyl ring at various interannular dihedral angles and the orientation of subsequent attack by an electron-deficient reactant is excellent, giving the experimentally obtained product in each case.

In the case of the condensation product of 1,3-cyclohexanedione, dimethylformamide, and phosphorus oxychloride, the calculations with the analogous compounds helped to provide insight into the lack of equilibration to get the thermodynamically more stable product as predicted by the calculations; namely, the energetic barrier between the product actually obtained and the thermodynamically more stable benzenoid product was predicted to be higher than those for other

competing reactions, such as decomposition and polymerization.

In the case of the condensation product of formaldehyde, hydrazine sulfate, and hydrogen peroxide, the only conclusion to be made from the calculations was that the thermodynamically more stable product was not formed. Experimentally, the product was observed to crystallize out of solution on formation and so this may block establishment of an equilibrium by which the thermodynamically more stable product may be obtained.

In the study of the importance of the effect of dipole stabilization on the stability of carbanions which contain adjacent heteroatoms with induced positive charges, it was found that the major stabilizing effect in systems containing Li as counterion is that of electrostatic attraction between the positively charged Li cation and the nearby atoms which had a formal negative charge: the two carbonyl oxygens, and the carbanionic carbon. Predictions were made about the relative stabilities of various lithiated systems, and of the contribution made to the stability of the system by each additional adjacent positively charged heteroatom. These predictions await experimental confirmation.

Overall, the calculations proved reasonably successful in providing insights into the problems studied, and they showed that it is possible to obtain good correlations and insights into actual problems encountered by an organic research group, without the use of supercomputers and/or lengthy calculations.

APPENDIX

The program used to perform the calculations on the compounds studied in this work is AM1/MNDO, which is part of the semi-empirical molecular orbital calculations program package, MOPAC. This program was chosen for a number of reasons: First, the program package is widely available to organic chemists and other interested parties, through the Quantum Chemistry Program Exchange at the University of Indiana; second, calculations made with the programs take up much less time than calculations made with ab initio programs; third, the calculated geometries and energies come very close to reproducing experimental results in test cases.

The formalism of the MNDO program is presented at length and in detail in [77JA4899], so the interested reader is referred to that reference for further details. The formalism of the AM1 program is much the same as that for MNDO, save for that the Hamiltonian operator is slightly modified in order to

correct for overestimation of the core-core repulsions. Details of this are given in [85JA3902], along with the parameters for AM1.

The parameterization for both AM1 and MNDO is designed to reproduce molecular geometries and heats of formation. Thirty reference molecules are used in the parameterization of MNDO, in a manner described in [77JA4899], to generate trial parameters, which are then optimized using a non-linear least-squares curve fitting program.

In Chapter V, calculations were reported on a series of lithiated carbanions. The parameters used for Li are given below:

Heat of formation data:

EHEAT	38.600	ΔH_f data
EISOLM	-5.128	"

Core-electron attractions:

VS	-5.390
VP	-3.540

One-electron integral data:

GSSM	7.300	$g_{\mu\nu}$
GPPM	5.0	"
GSPM	5.43	"
GP2M	4.52	"

HPPM	0.83	h_{uv}
USSM	-5.128	one-center
UPPM	-2.7217	energy terms
Resonance integral factors:		
BETASM	-1.35	
BETAPM	-1.35	" "
Orbital exponents:		
ZSM	0.70238	orbital exponent
ZPM	0.70238	" "
Exponential fitting factor for Li atom:		
ALPM	1.25014	
Quantities used in estimation of two-electron integrals:		
1. Charge Separation terms:		
DDM	2.05497823	dipole
QQM	1.7437069	quadrupole
2. Additive terms used in Ohno-Klopman or Mataga-Nishimoto Equations:		
AMM	0.2682837	monopole term
ADM	0.22697935	dipole term
AQM	0.26145812	quadrupole term

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Letter Codes for Journal Titles

<u>Code</u>	<u>Full Title</u>
A	Justus Liebigs Annalen
AC	Acc. Chem. Res.
ANE	Angew. Chem., Int. Ed. Engl.
BF	Bull. Soc. Chim. Fr.
CA	Chemical Abstracts

CB	Chem. Ber.
CJC	Can. J. Chem.
CPL	Chem. Phys. Lett.
F	Trans. Faraday Soc.
J(P2)	J. Chem. Soc., Perkin Trans. II
JA	J. Am. Chem. Soc.
JCP	J. Chem. Phys.
JMC	J. Organomet. Chem.
JO	J. Org. Chem.
MI	Miscellaneous (book)
PC	Personal Communication
S	Science
T	Tetrahedron
TL	Tetrahedron Lett.
ZP	Z. Phys.
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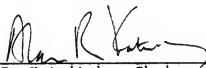
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BIOGRAPHICAL SKETCH

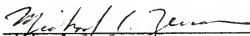
Hudson H. Luce was born in Scranton, Pennsylvania, on June 5, 1957. He was raised in Topeka, Kansas, and attended the University of Kansas in Lawrence, where he obtained a Bachelor of Science degree in chemistry. He then went on to Emory University in Atlanta, Georgia, and obtained a Master of Science degree in chemistry, studying under Professor Dennis C. Liotta. In 1983, he came to the University of Florida to work toward his Ph.D. in chemistry, working under Professor Alan R. Katritzky, in collaboration with Professor Michael C. Zerner. His research interests are in the application of theoretical methods to problems in heterocyclic organic chemistry, and the application of computational techniques, from numerical analysis to AI, to those problems. His outside interests are photography and bicycle racing, as well as listening to, and commenting on, music by local rock and roll bands.

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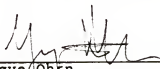
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December, 1987

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